Occupational determinants of pancreatic cancer

Anneli Ojajärvi

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Supervised by

Docent Timo Partanen
Tampere School of Public Health
University of Tampere,
Tampere, Finland

Professor Timo Hakulinen
Department of Public Health,
University of Helsinki,
Helsinki, Finland
and
Institute for Statistical and Epidemiological Cancer Research
Finnish Cancer Society

Reviewed by

Professor Anssi Auvinen
Tampere School of Public Health
University of Tampere
Tampere, Finland

Professor Esa Läärä
Department of Mathematical Sciences
Division of Statistics
University of Oulu
Oulu, Finland

Opponent

Professor Matti Hakama
Tampere School of Public Health
University of Tampere
Tampere, Finland

To Olli, Jaakko and Alma

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ABSTRACT

Objective and background. Tobacco smoking, pancreatitis and diabetes mellitus are the only known causes of pancreatic cancer, leaving ample room for yet unidentified determinants. This is an empirical study on a Finnish data on occupational exposures and pancreatic cancer risk, and a non-Bayesian and a hierarchical Bayesian meta-analysis of data on occupational factors and pancreatic cancer.

Methods. The case-control study analyzed 595 incident cases of pancreatic cancer and 1,622 controls of stomach, colon, and rectum cancer, diagnosed 1984-1987 and known to be dead by 1990 in Finland. The next-of-kin responded to a mail questionnaire on job and medical histories and lifestyles. Meta-analysis of occupational risk factors of pancreatic cancer started off with 1,903 identified studies. The analyses were based on different subsets of that database. Five epidemiologists examined the reports and extracted the pertinent data using a standardized extraction form that covered 20 study descriptors and the relevant relative risk estimates. Random effects meta-analyses were applied for 23 chemical agents. In addition, hierarchical Bayesian models for meta-analysis were applied to the occupational data of 27 job titles using job exposure matrix as a link matrix and estimating the relative risks of pancreatic cancer associated with nine occupational agents.

Results. In the case-control study, logistic regressions revealed excess risks of pancreatic cancer associated with occupational exposures to ionizing radiation, nonchlorinated solvents, and pesticides. Chlorinated hydrocarbon solvents and related compounds, used mainly in metal degreasing and dry cleaning, are emerging as likely risk factors of pancreatic cancer in the non-Bayesian and the hierarchical Bayesian meta-analysis. Consistent excess risk was found for insecticides, and a high excess for nickel and nickel compounds in the random effects meta-analysis but not in the hierarchical Bayesian meta-analysis.

Conclusions. In this study occupational exposure to chlorinated hydrocarbon solvents and related compounds and insecticides increase risk of pancreatic cancer. Hierarchical Bayesian meta-analysis is applicable when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents. A job-exposure matrix or a formal expert assessment system is necessary in this situation.

LIST OF ORIGINAL COMMUNICATIONS

The thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kauppinen T, Partanen T, Degerth R, Ojajärvi A. Pancreatic cancer and occupational exposures. Epidemiology 1995;6:498-502.

II Ojajärvi IA., Partanen TJ, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, KauppinenTP Kogevinas M, Porta M, Vainio HU, Weiderpass E, Wesseling CH. Occupational exposures and pancreatic cancer: a meta-analysis. Oc cup Environ Med 2000;57:316-24.

III Ojajärvi A., Partanen T, Ahlbom A, Boffetta P, Hakulinen T, Jourenkova N, Kauppinen T, Kogevinas M, Vainio H, Weiderpass E, Wesseling C. Risk of pancreatic cancer in workers exposed to chlorinated hydrocarbon solvents and related com pounds: a meta-analysis. Am J Epidemiol 2001;153:841-50.

IV Ojajärvi A., Partanen T, Ahlbom A, Hakulinen T, Kauppinen T, Weiderpass E, Wesseling C. Estimating the relative risk of pancreatic cancer associated with exposure agents from job title data with hierarchical Bayesian meta-analysis. Submitted

ABBREVIATIONS

AICR	American Institute of Cancer Research
ALHC	Aliphatic and alicyclic hydrocarbons
CKK	Chelocytoskinine-pancreazymin
CHC	Chlorinated hydrocarbon
CI	Confidence interval
CR	Chromium
CrI	Credible interval
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
EEF	Etiological fraction among exposed
FINJEM	Finnish job exposure matrix
FUNG	Fungicides
HB	Hierarchical Bayesian
HMSO	Her Majesty's Stationery Office
HR	Hazard ratio
IH	Industrial hygienist
IARC	International Agency for Research on Cancer
INSC	Insecticides
JEM	Job exposure matrix
MCMC	Markov chain Monte Carlo
MOR	Mortality odds ratio
MRR	Meta-relative risk
NI	Nickel and nickel compounds
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
PCB	Polychlorinated biphenyl
PCMR	Proportional cancer mortality ratio
PEF	Population etiological fraction
PMR	Proportional mortality ratio
RE	Random effects
RR	Relative risk
SIL	Silica dust
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
TDE	Tetrachlorodiphenyletane
WOOD	Wood dust

1. INTRODUCTION

The pancreas is about 15 cm long organ and is located behind the stomach. It has two functions: to send insulin into the bloodstream to control the amount of sugar in the blood, and to send pancreatic juice into the intestine to help digest food. About 95% of all pancreatic cancers derive from the exocrine component, which transports the pancreatic juice. Endocrine tumors arising in islet cells constitute about 5% of all pancreatic cancers (Brennan et al., 1993).

According to Ferley et al. (2001) approximately 200,000 new cases of pancreatic cancer (International Classification of Diseases: code 157 in 9th revision and code C25 in 10th revision) were annually diagnosed worldwide in 2000. In Finland, the number was 878 in 2004 (www.syoparekisteri.fi).

Results of the epidemiological studies of associations between risk of pancreatic cancer and occupational branches and job titles are heterogeneous and inconsistent, and exposures shared by high-risk jobs are hard to identify (Partanen et al., 1994; Ji et al., 1999; Kernan et al., 1999; Alguacil et al., 2000a; Alguacil et al., 2000b; Alguacil et al., 2003a). The population etiologic fraction of pancreatic cancer due to occupational exposures was estimated at 26% in Montreal, Canada (Siemiatycki et al., 1991). No single occupational exposure has been confirmed to increase the risk of pancreatic cancer with high probability. Most of the associations with single chemical agents emerged in one study only. The separation between spurious and causal associations presents serious difficulties.

This study investigated the relationship between occupational determinants and pancreatic cancer, first in the case-control study based on Finnish data, and secondly in meta-analyses of occupational agents and occupations by using random effects and hierarchical Bayesian models for meta-analysis. In the hierarchical Bayesian models, this study also evaluates the feasibility of use of a job-exposure matrix in meta-analysis.

2. A LITERATURE REVIEW

2.1 Pancreatic cancer

2.1.1 Descriptive epidemiology of pancreatic cancer

Incidence and geographical distribution

The populations of "developed" countries appear to carry a higher burden of pancreatic cancer than those of less developed countries. Regionally, the highest annual age-adjusted incidence rates per 100 000 person years in 2000 were estimated among black males in Connecticut, USA (14.7) and Michigan, Detroit, USA (13.7), and among males in Hungary (12.3) and Latvia (12.1) (Ferlay et al., 2001; Parkin et al., 2002). The lowest rates were reported among both genders for Western Africa, South Central Asia and Melanesia (Ferlay et al. 2001). No consistent urban-rural gradient is discernible (Parkin et al., 1993). Mortality rates follow closely incidence rates because of rapid fatality of pancreatic cancer.

Time trends

Incidence rates have been rising in developed countries since the 1960s and leveled or leveling off in populations such as those of the Nordic countries, Scotland, Northern Ireland (Coleman et al., 1993; Estéve et al., 1993; Fernandez et al., 1994) and USA (Zheng et al., 1995). The increase may be attributable to increased sensitivity of modern preoperative diagnostic methods, to the higher accessibility of people to the health system, and to better registration procedures, but an actual increase in incidence appears to have taken place (Estéve et al., 1993).

Age and gender distribution

Incidence and mortality rates increase steeply among people 40-70 years of age. Incidence of pancreatic cancer is higher among men than women. The average age-adjusted male-to-female ratio of pancreatic cancer incidence is about 1.5 for more developed countries and 1.4 for less developed countries (Ferlay et al., 2001). It was 1.46 in Finland in 2004 (www.syoparekisteri.fi). The age-adjusted incidence ratio between more developed and less developed countries was 2.8 for men and 2.5 for women during the same time period (Ferlay et al., 2001).

Socioeconomic status

Pancreatic cancer is not consistently associated with socioeconomic status within national populations (Faggiano and Partanen 1997; Kogevinas et al., 1997b).

2.1.2 Determinants of pancreatic cancer

Migrant studies suggest that environmental factors influence the risk of pancreatic cancer. Studies have been conducted on Italian migrants, on migrants from Europe to Australia and Israel, and from Mexico to Los Angeles. Pancreatic cancer rates have usually shifted from the level of the country of origin toward that of the host country (Geddes et al., 1993; Geddes et al., 1994).

Pancreatic cancer is strongly related to tobacco smoking, which carries an average of 2-3 fold relative risk that increases with the number of pack-years of smoking (Lund Nilsen and Vatten, 2000). The association between tobacco smoking and pancreatic cancer is weaker than that between tobacco smoking and lung cancer. Acute and chronic pancreatitis, type II diabetes and past gastric surgery have been associated with pancreatic cancer (Lowenfels et al., 1997; Gold and Goldin, 1998; Malka et al., 2002; Huxley et al. 2005). A number of dietary factors have been associated with pancreatic cancer (Gold and Goldin, 1998). Table 1 illustrates nonoccupational risk factors of pancreatic cancer.

Workplace exposures may be causally associated with pancreatic cancer (Weiderpass et al., 1998). Results of a large number of epidemiological studies that have linked industries and jobs with pancreatic cancer are heterogeneous and inconsistent. No single occupational agent has been confirmed to increase the risk of pancreatic cancer.

TABLE 1. Risk factors of pancreatic cancer.

	High risk	Moderate risk	Low risk
General factors:			
Age	Old	Middle	Young
Gender	Male		Female
Geographic location	Developed country		Developing country
Lifestyle factors:			
Smoking	Heavy	Light	No
Body mass index	Obese	High	Normal/Low
Medical factors:			
Type II diabetes duration	< 5yrs	> 4 yrs	No diabetes
Pancreatitis	Yes		No
Helicobacter	Yes		No
Dietary factors:			
Intake level of			
vegetables	Low		High
fruits	Low		High
fibers	Low		High
carbohydrates	High		Low
proteins	High		Low
Other factors:			
Family history	Yes		No

Lifestyles

Tobacco smoking

Tobacco smoking is the single major substantiated cause of exocrine pancreatic cancer (Silverman et al., 1994). Results from over 30 studies are available. With the exception of the indeterminate results of three studies (La Vecchia et al., 1987; Pisani, 1994; Shibata et al., 1994), all are consistent with cigarette smoking as a cause of pancreatic cancer (Ishii et al., 1973; Williams and Horm, 1977; Jick and Dinan, 1981; Severson et al., 1982; Hsieh et al., 1986; Mack et al., 1986; Norell et al., 1986a; Wynder et al., 1986; Carstensen et al., 1987; Hiatt et al., 1988; Mills et al., 1988; Cuzick and Babiker, 1989; Ferrarroni et al., 1989; Olsen et al., 1989; Farrow and Davis, 1990; Tomioka et al., 1990; Baghurst et al., 1991; Howe et al., 1991; Ghadirian et al., 1991b; Bueno de Mesquita et al., 1991; Lyon et al., 1992; Friedman and van den Eeden, 1993; Zatonski et al., 1993; Zheng et al., 1993; Silverman et al., 1994; Ji et al., 1995; Fernandez et al., 1996; Fuchs et al. 1996; Harnack et al., 1997; Muscat et al., 1997; Partanen et al., 1997; Coughlin et al., 2000; Lund Nilsen and Vatten, 2000; Villeneuve et al., 2000; Chiu et al., 2001; Silverman, 2001; Stolzenberg-Solomon et al., 2001b; Inoue et al., 2003). A dose-response relationship with the number of cigarettes per day was observed in several studies (Farrow and Davis, 1990; Howe et al., 1991; Zheng et al., 1993; Muscat et al., 1997; Partanen et al., 1997; Coughlin et al., 2000; Lund Nilsen and Vatten, 2000; Chiu et al. 2001; Stolzenberg-Solomon et al., 2001b; Inoue et al., 2003). High daily doses of tobacco smoke have been associated with risk ratios of the order of 2-3, occasionally reaching values over 5. Several studies have found a positive dose-response association with the number of pack years of smoking and pancreatic cancer (Bueno de Mesquita et al., 1991; Fuch et al. 1996; Harnack et al., 1997; Lund Nilsen and Vatten, 2000; Villeneuve et al., 2000; Stolzenberg-Solomon et al., 2001b). In a cohort study among Finnish male smokers (Stolzenberg-Solomon et al., 2001b), over 49 pack-years of cigarette smoking, compared with less than 22 pack-years, was associated with pancreatic cancer incidence with hazard ratio (HR) 1.67; 95 % confidence interval (CI) 1.04-2.72; trend p 0.04. Two studies have found a strong increased association between smokeless tobacco use and risk of pancreatic cancer (Alguacil and Silverman, 2004; Boffetta et al., 2005). The estimated attributable risk from smoking (the proportion of pancreatic cancer caused by smoking) ranges between 26% and 52% in the United States (Moolgavkar and Stevens, 1981; Gold et al., 1985; Mack et al., 1986; Silverman et al., 1994); in northern Italy, it was 20% for men and 5% for women (Fernandez et al., 1996). Giving up smoking would substantially reduce the subsequent incidence of pancreatic cancer (Mulder et al., 2002).

Alcoholic beverages

Several epidemiological studies, including 30 studies in the review study conducted by American Institute of Cancer Research (AICR) (1997) and a number of further studies (La Vecchia et al., 1987; Gorham et al., 1988; Ferrarroni et al., 1989; Bouchardy et al., 1990; Partanen et al., 1997; Villeneuve et al., 2000; Silverman, 2001), found an association between alcohol consumption and risk of pancreatic cancer. Nine cohort studies yielded a consolidated risk ratio (RR) of 1.2 (95% CI 0.9-1.4) for heavy consumers (Velema et al., 1986). Silverman et al. (1995) found an increased risk among heavy alcohol drinkers in the United States, particularly among black non-smokers. However, 22 studies with a reasonable power to detect a positive association between alcohol consumption and risk of pancreatic cancer failed to do so (La Vecchia et al., 1987; Gorham et al., 1988; Ferrarroni et al., 1989; Bouchardy et al., 1990; AICR, 1997). On occasion the excess may have been a result of confounding by tobacco smoking (Lyon et al., 1992). According the review of AICR (1997) high alcohol consumption probably has no relationship with the risk of pancreatic cancer. Confounding by tobacco smoking is possible in studies that did not adjust for smoking.

Coffee consumption

Seven studies reviewed by AICR (1997) and one further study (Gullo et al. 1995) found relative risks of pancreatic cancer of the order of 2-3 for those who drank 5 or more cups daily. A dose-response was found in some studies. Confounding from smoking may have been possible in some of the studies. Nineteen studies in the study of AICR (1997) and Elinder et al. (1981), Jick and Dinan (1981), Heuch et al. (1983), Whittemore et al. (1983), Stensvold and Jakobsen (1994), Partanen et al. (1995), and Villeneuve et al. (2000) failed to reproduce the coffee association. Coffee consumption may not have an independent effect but it is possible that coffee potentiates or decreases the effect of other risk factors, possibly depending on metabolizing phenotypes (Vineis, 1993). Confounding by tobacco smoking may be possible in studies without control of such potential confounding.

Diet

Eighteen case-control studies (Falk et al., 1988; Raymond et al., 1987; Goto et al., 1990; Negri et al., 1991; AICR, 1997; Silverman et al. 1998; Stolzenberg-Solomon et al., 1999; Stolzenberg-Solomon et al., 2001b; Stolzenberg-Solomon et al., 2002a) and two prospective cohort studies (AICR, 1997) reported a decreased pancreatic cancer risk at high consumption levels of vegetables or fruit (Odds Rations[ORs] ranged 0.3-0.9 and RRs 0.6-0.9). For meat and meat products; seven case-control studies (Goto et al., 1990; AICR, 1997) and three cohort studies (AICR, 1997) reported a positive association with pancreatic cancer. One case-control study (AICR, 1997) have reported a strong increase in the risk with a high consumption (smoking adjusted OR 2.5, 95%CI 1.2-5-1 for >10 vs <5 servings meat per week). Four case-control studies (AICR, 1997; Silverman et al., 1998) and one prospective cohort study (Michaud et al., 2003) failed to do so, and one case-control study (AICR, 1997) suggested protection by high lean pork meat intake (OR 0.6, 95% CI 0.3-1.2). The strength of the consolidated evidence on excess associated with meat consumption is only moderately convincing.

Total energy, macronutrients and dietary fiber. Most of the current evidence on pancreatic cancer and intake of total energy and macronutrients comes from a multicentric case-control study conducted in Adelaide, Australia; Toronto and Montreal, Canada; Opole, Poland; and the Netherlands (AICR, 1997). A pooled analysis revealed an increased risk at high levels of total energy intake (ORs 1.2, 1.2, 2.0 and 2.1; p>0.0001 for trend) and at high intakes of total carbohydrates (OR 1.7, 95% CI 1.3-2.4 for the highest vs the lowest quartile)(AICR, 1997). An evidence of decrease in pancreatic cancer risk at high intakes of dietary fiber was revealed. The effects of total energy intake and macronutrients have been investigated in three case-control studies (AICR, 1997). A French study found an excess risk for high intake of total fat, but the finding was unadjusted for total energy intake (AICR, 1997). The western Washington, United States, and Athens, Greece, studies did not find associations for either total or saturated fat or total carbohydrates (AICR, 1997). For protein, nine case-control studies (including the multicentric study) failed to show a clear association with pancreatic cancer risk, while one study reported an excess at high intake levels (AICR, 1997).

Micronutrients. A negative association between pancreatic cancer risk and intake levels of vitamin C has been repeatedly reported (Falk et al., 1988; Howe et al., 1990; Ghadirian et al., 1991c; Zatonski et al., 1991; Kalapothaki et al., 1993). Associations with intake levels of carotenoids were generally weaker. One prospective cohort study on serum concentrations of carotenoids (Comstock et al., 1991) found a strong inverse association with serum levels of lycopene.

Obesity

Six studies (Friedman and van den Eeden, 1993; Moller et al., 1994; Silverman et al., 1998; Michaud et al., 2001; Silverman, 2001; Pan et al., 2004; Fryzek et al., 2005) reported positive associations between obesity and pancreatic cancer risk, which were however not confirmed in other studies (Mack et al., 1986; Bueno de Mesquita et al., 1990; Howe et al., 1990; Ghadirian et al., 1991c; Bueno de Mesquita et al., 1992; Kalapothaki et al., 1993; Pezzilli et al., 2005). In a recent meta-analysis (Berrington de Gonzalez et al., 2003), including six case-control and eight cohort studies, the meta-relative risk (MRR) for pancreatic cancer per unit increase in body mass index (BMI) was estimated to be 1.02 (95% CI: 1.01-1.03).

Use of aspirin

Two cohort studies found a decreased pancreatic cancer risk in aspirin users, while two case-control studies failed to confirm this association (Baron, 2004), one cohort study suggesting that the use of aspirin would increase the risk (Baron, 2004).

Medical conditions

Helicobacter pylori have been sporadically associated with pancreatic cancer (Gold and Goldin, 1998; Stolzenberg-Solomon et al., 2001a). For two additional conditions, pancreatitis and type II diabetes mellitus, a fair number of studies are available (Gold and Goldin, 1998; Huxley et al., 2005).

Pancreatitis

Pancreatitis, both chronic and acute, is frequently caused by heavy consumption of alcohol. Pancreatitis has been linked with pancreatic cancer (Ansari and Burch, 1968; Lowenfels, 1984; Velema et al., 1986; Gorham et al., 1988; Lowenfels, 1993; Fernandez et al., 1995¸ Malka et al., 2002). In a cohort study (Malka et al., 2002), the standardized incidence ratio (SIR) was 26.7 (95% CI 7.3-68.3). As this condition is rare, population etiologic fraction is low, estimated at 0.1-5 percent (Fernandez et al., 1995). Lowenfels et al (1997) have reported an increased risk in hereditary chronic pancreatitis.

Diabetes mellitus

Huxley et al. (2005) updated a meta-analysis of pancreatic cancer and type II diabetes (Everhart and Wright, 1995). Ten out of 17 case-control studies and all 19 cohort studies found an association between pancreatic cancer and diabetes mellitus diagnosed at least one year before the diagnosis of pancreatic cancer. The meta-relative risk (MRR) was negatively associated with the duration of diabetes mellitus (MRRs 2.1, 1.5 and 1.5). Subjects who had had diabetes diagnosed less than five years had 50% higher MRR than five or longer diagnosed. Stolzenberg-Solomon et al. (2002b) reported a strong association between pancreatic cancer and self reported diabetes mellitus in a cohort study of Finnish male smokers.

Helicobacter pylori

An association between helicobacter pylori and pancreatic cancer has been reported in few studies, but the evidence remains insufficient (Raderer et al., 1998; Stolzenberg-Solomon et al., 2001a; Manes et al., 2003).

Family history and genetic factors

While two studies found familial clustering of pancreatic cancer, the data are inconsistent. Ghadirian et al. (1991a) reported that 7.8% of their pancreatic cancer patients had a family history of pancreatic cancer, compared with 0.6% in its matched controls in the Francophone community in Montreal, Canada. Another positive suggestion comes from Italy (La Vecchia et al., 1992). Lynch et al. (1992) reported a family cluster with pancreatic cancer through three generations. The genetic component in the familial aggregation of pancreatic cancer has been estimated at 2 % in northern Italy (Fernandez et al., 1996). Silverman (2001) found high elevated risks of pancreatic cancer for subjects with a family history of cancers of the pancreas, colon or ovary.

Hereditary chronic pancreatitis appears to be associated with pancreatic cancer (Tersmette et al., 2001; Malka et al., 2002). The role of genetic polymorphisms of metabolic enzymes in the modification of pancreatic cancer risk is not clear (Malats et al., 1997).

Pancreatic cancer has the highest frequency (75%-85%) of K-ras mutations among all human neoplasms. Environmental factors that have been associated with K-ras mutations in pancreatic cancer are alcohol consumption, tobacco smoking (Malats et al., 1997; Porta et al., 1999b), coffee drinking (Porta et al., 1999a; Porta et al., 1999b), and organochlorines (Porta et al., 1999c). In the first study on occupational exposures and K-ras mutations in pancreatic cancer Alguacil et al. (2002) found a strong association between K-ras mutations and organic solvents. Alguacil et al. (2003b) also observed an association between K-ras mutations and occupational exposure to dyes and organic pigments (OR 4.8), lead, polycyclic aromatic hydrocarbons (PAHs), benzo[a]pyrene, gasoline, nickel, inhalatory exposure to chromium, and sedentary work.

Occupational factors

Some workplace exposures may increase the risk of pancreatic cancer. Results of a fair number of epidemiological studies that have linked industries and job titles with an excess of pancreatic cancer are heterogeneous and inconsistent, and exposures shared by alleged high-risk jobs are hard to identify.

Job titles

Laundry and dry cleaning operators. Partanen et al. (1994) found excess risk (OR 2.4. 95% CI 0.3-17) of pancreatic cancer among laundry and dry cleaners in a case-control study. Out of nine standardized incidence ratio (SIR) and standardized mortality ratio (SMR) studies, three (Lynge and Thygensen, 1990; Ruder et al., 1994; Ruder et al., 2001) found a high excess; four (Brown and Kaplan, 1987; Blair et al., 1990; Pukkala, 1995; Andersen et al., 1999) reported smaller excesses, while two (Norell et al., 1986b; Travier et al., 2003) failed to find an excess. Hrubec et al. (1992) observed a weak positive association in their cohort mortality study. Out of nine proportional mortality ratio (PMR) or mortality odds ratio (MOR) studies, four (Katz and Jowett, 1981; Dubrow, 1984; Petrone, 1988; Gallagher et al., 1989) found a weak positive association, while five (Duh and Asal, 1984; Nakamura, 1985; Olsen and Jensen, 1987; Milham, 1997; Walker et al., 1997) reported a negative association.

Machine and automobile manufacture workers. Alguacil et al. (2000b) found an excess risk (OR 3.4) of pancreatic cancer for Spanish machinery mechanics and fitters in a case-control study. Out of eight SMR studies, four (Eisen et al., 1992; Garabrant et al., 1988; Rotimi et al., 1993; Eisen et al., 2001) observed high excesses; two (Delzell et al., 1993; Beall et al., 1995) a low positive risk; while two (Costa et al., 1989; Rushton, 1993) faild to show an excess. Out of seven PMR/MOR-studies one (Vena et al., 1985) had a strong positive association; five (Chiazze et al., 1984; Dubrow, 1984; Mallin et al., 1986; Park et al., 1988; Silverstein et al., 1988) a weak positive; and one (Milham, 1997) a weak negative association.

Printing workers. Out of seven case-control studies five (Pietri et al., 1990,; Siemiatycki et al., 1991; Ji et al., 1999; Kernan et al., 1999; Alguacil et al., 2003a) found high excesses for printing workers (OR ranged 1.2 - 5.2). Partanen et al. (1994) found a weak positive association, while the Bouchardy et al. study (2002) was nonpositive. In cohort studies, Coggon et al. (1986a) found a positive and Hrubec et al. (1992) a negative association. One (Minder and Beer-Porizek, 1992) of the seven SIR/SMR-studies found a high excess; four (Paganini-Hill et al., 1980; Malker and Gemne, 1987; Leon, 1994; Lynge et al., 1995) reported a smaller positive association with pancreatic cancer; while two (Michaels et al., 1991; Pukkala, 1995) were nonpositive. Out of the nine PMR/MOR-studies, Lloyd et al. (1977) found a high excess, while the remaining studies (Greene et al., 1979; Dubrow, 1984; Zoloth et al., 1986; Magnani et al., 1987; Olsen and Jensen, 1987; Gallagher et al., 1989; Costa et al., 1995; Milham, 1997) reported smaller excesses.

Pulp and paper workers. Four case-control study studies (Wingren et al., 1991; Partanen et al., 1994; Kernan et al., 1999; Alguacil et al., 2003a) reported moderately low excesses (OR 1.3 - 1.4), and one (Siemiatycki et al., 1991) a weak negative association for pulp and paper workers. Out of 12 SIR/SMR-studies, Pukkala (1995) reported a strong positive association; four studies (Norell et al., 1986b; Henneberger et al., 1989; Coggon et al., 1997; Rix et al., 1998) had a weaker positive; and seven (Robinson et al., 1986; Lanes et al., 1993; Sala-Serra et al., 1996; Wong et al., 1996; Band et al., 1997; Szadkowska-Stanczyk et al., 1997; Matanoski et al., 1998) a negative association. Out of the five PMR/MOR studies, Magnani et al. (1987) found a high excess, while in three studies (Milham and Demers, 1984; Schwartz, 1988; Milham, 1997) the excess was smaller, and two (Dubrow, 1984; Solet et al., 1989) reported deficits.

Textile workers. Out of eight case-control studies three (Partanen et al., 1994; Alguacil et al., 2000b; Zhang et al., 2005) found a high excess risk for pancreatic cancer (OR ranged 5.8 - 11.5) and the rest of studies (Pietri et al., 1990; Siemiatycki et al., 1991; Ji et al., 1999; Kernan et al., 1999; Boychardy et al., 2002) a smallest excess risk (OR ranged 1.1 - 1.9). Pukkala (1995) observed a positive association in a SIR-study and Delzell et al. (1989) a negative association in s SMR-study. Out of four PMR/MOR-studies two (Dubrow, 1984; Olsen and Jensen, 1987) found a positive association with pancreatic cancer and two (Delzell and Drufferman, 1983; Dubrow and Gute, 1988) failed to do it.

Job titles with reported excess risk of pancreatic cancer at least two epidemiological studies are listed in Table 2. Various chemical exposures have been and are present in these job titles.

Occupational agents

No single occupational agent has been confirmed to increase the risk of pancreatic cancer with reasonable likelihood. The bulk of the occupational chemical agents that have been associated with excess risk in the epidemiological studies emerged in one study only, suggesting that many of the associations may be artifacts from confounding or chance. If no additional information, e.g. from animal bioassays, is available, the distinction between spurious and causal associations presents formidable difficulties, given the general uncertainty about the causative agents involved in the development of pancreatic cancer. The pervasive lack of individual historical exposure data in epidemiological studies of cancers with long latency periods is an additional problem in the interpretation of the findings. Also, many reported "agents" have in fact been more or less heterogeneous groups of agents such as "pesticides" or "organic solvents".

Chlorinated hydrocarbon solvents have been associated with high excess risk of pancreatic cancer in two case-control studies (Kernan et al., 1999; Hoppin et al., 2000), in which ORs were 2.9 and 4.2, respectively, and in three SIR/SMR-studies three (Benson and Teta, 1993; Yassi et al., 1994; Anttila et al., 1995), in which SIR/SMR ranged from 2.0 to 4.9. Lower excesses were found in two case-control studies (Greenland et al., 1994; Alguacil et al., 2000a), in five SIR/SMR-studies (Nakamura, 1983; Smulevich et al., 1988; Wong et al., 1991; Tomenson et al., 1997; Chang et al., 2003), and in two PMR-studies (Chiazze and Ference, 1981; Magnani et al., 1987). A weak negative association was reported in one case-control study (Siemiatycki et al., 1991), and in seven SIR/SMR-studies (Brown, 1987; Simonato et al., 1991; Spirtas et al., 1991; Sinks et al., 1992; Lanes et al., 1993; Axelson et al., 1994; Gibbs et al., 1996).

Pesticides have been associated with high risk of pancreatic cancer in five case-control-studies (Garabrant et al., 1993; Kernan et al., 1999; Alguacil et al., 2000a; Ji et al., 2001; Clary and Ritz, 2003), in one SMR-study (Beard et al., 2003), and in one RR-study (Cantor and Silberman, 1999). ORs ranged from 1.5 to 21.0, SMR was 1.9 and RR 2.7. Smaller excesses were found in one case-control study (Fryzek et al., 1997), in five SIR/SMR-studies (Swaen et al., 1992; Asp et al., 1994; Lee et al., 1996; Satihiakumar et al., 1996; Hooiveld et al., 1998) and in one RR-study (Ramlow et al., 1996). Deficits were found in one case-control study (Siemiatycki et al., 1991), in five SIR/SMR-studies (Lynge, 1985; Coggon et al., 1986b; Ott et al., 1987; Brown et al., 1992; Kogevinas et al., 1997a) and in two PMR-studies (Magnani et al., 1987; Cocco et al., 1997).

Polycyclic aromatic hydrocarbons have been associated with high excess risk in one case-control study (Romudstad et al., 2000; OR 6.38, 95% CI 1.3-30.6 in the highest exposure category) and in one incidence study (Weiderpass et al., 2003), in which RR was 1.5. Two case-control studies (Siemiatycki et al., 1991; Alguacil et al., 2000a) and two SIR/SMR-studies (Cammarone et al., 1986; Moulin et al., 1989) reported smaller excesses.

Nine occupational agents have been associated with excess risk in more than two studies: pesticides in nine studies; chlorinated hydrocarbon solvents in six studies; asbestos and polycyclic aromatic hydrocarbons in four studies; chromium and chromium compounds, electromagnetic fields and low frequency electromagnetic fields in three studies; ionization radiation, and nickel and nickel compounds in two studies (Table 2).

TABLE 2. Job titles and occupational agents with reported excess risks of pancreatic cancer at least two epidemiological studies.

Job
Administration, science, managers (Lin and Kessler, 1981; Falk et al., 1990; Siemiatycki et al., 1991; Partanen et al., 1994; Kernan et al., 1999; Alguacil et al., 2003a)
Aluminium reduction, aluminium workers (Rockette and Arena, 1983; Mur et al., 1987; Carta et al., 1992)
Auto mechanics; gas station and garage workers (Lin and Kessler, 1981; Hansen, 1989)
Chemical workers (Mancuso and El Attar, 1966; Hanis et al., 1982; Bond et al., 1985; Hirayama, 1989)
Chemists (Li et al., 1969; Cordier, 1990; Cordier et al., 1995; Milham, 1997)
Cooks (Siemiatycki et al., 1991; Andersen et al., 1999; Alguacil et al., 2003a)
Electrical and electronic workers (Andersen et al., 1999; Alguacil et al., 2003a)
Foodstuff workers (Magnani et al., 1987; Carstensen et al., 1990; Siemiatycki et al., 1991; Andersen et al., 1999; Alguacil et al., 2003a)
Farmers (Burmeister, 1981; Blair et al., 1993; Cerhan, 1998; Alguacil et al., 2000b; Lee et al., 2002)
Hairdressers, barbers (Pukkala, 1995; Lamba et al., 2001)
Laundry and dry cleaning operators (Lynge and Thygensen, 1990; Ruder et al., 1994; Andersen et al., 1999; Ruder et al., 2001)
Leather and footwear workers (Decoufle et al., 1977; Edling et al., 1986; Constantini et al., 1989; Siemiatycki et al., 1991)
Machine and automobile manufacture workers (Vena et al., 1985; Mallin et al., 1986; Silverstein et al., 1988; Alguacil et al., 2000b; Eisen et al., 2001)
Maintenance personnel, charworkers (Siemiatycki et al., 1991; Andersen et al., 1999; Bouchardy et al., 2002; Alguacil et al., 2003a)
Motor vehicle drivers (Andersen et al., 1999; Bouchardy at al., 2002; Alguacil et al., 2003a)
Painters, lacquerers (Pukkala, 1995; Alguacil et al., 2000b; Brown et al., 2002)
Printing workers (Decoufle et al., 1977, Lloyd et al., 1977; Zoloth et al., 1986; Magnani et al., 1987; Mallin et al., 1989; Siemiatycki et al., 1991; Leon 1994; Alguacil et al., 2003a)
Pulp and paper workers (Bross et al., 1978; Magnani et al., 1987; Henneberger 1989; Wingren et al., 1991; Pukkala 1995; Wild et al., 1998)
Refinery workers (Gallagher et al., 1989; Pickle and Gottlieb 1980; Thomas et al., 1980; Siemiatycki et al., 1991; Shallenberger et al., 1992; Dement et al., 1998; Kernan et al., 1999)
Rubber industry workers (Monson and Fine 1978; Delzell et al., 1981; Szeszenia Dabrowska et al., 1991; Solovena 1992)
Seafarers, sailors, seamen (Andersen et al., 1999; Saarni et al., 2002)
Textile workers (Bross et al., 1978; Olsen and Jensen 1987; Partanen et al., 1994; Ji 1999; Alguacil et al., 2000b; Zhang et al., 2005)
Woodworkers (Kawachi et al., 1989; Bouchardy et al., 2002)

Agent
Asbestos (Selikoff and Seidman 1981; Seidman, 1986; Szeszenia Dabrowska et al., 1988; Falk et al., 1990)
Chlorinated hydrocarbon solvents (Hearne et al., 1990; Benson and Teta, 1993; Yassi et al., 1994;

Anttila et al., 1995; Kernan et al., 1999; Hoppin et al., 2000)
Chromium and chromium compounds (Franchini et al., 1983; Magnani et al., 1987; Weiderpass et al., 2003)
Electromagnetic fields (Tynes et al., 1992; Ji et al., 1999; Weiderpass et al., 2003)
Ionizing radiation (Polednak et al., 1983; Magnani et al., 1987)
Low frequency electromagnetic fields (Tynes et al., 1992; Ji et al., 1999; Weiderpass et al., 2003)
Nickel and nickel compounds (Siemiatycki et al., 1991; Weiderpass et al., 2003)
Pesticides (Alavanja et al., 1990; Garabrant et al., 1992; Garabrant et al., 1993; Forastiere et al., 1993; Cantor and Silberman, 1999; Alguacil et al., 2000a; Ji et al., 2001; Clary and Ritz, 2003; Beard et al., 2003)
Polycyclic aromatic hydrocarbons (Siemiatycki et al., 1991; Romundstad et al., 2000a; Romundstad et al., 2000b; Weiderpass et al., 2003)

2.2 Job-exposure matrix

Job-exposure matrices (JEMs) were developed to translate job titles to occupational agents occurring in different jobs. A number of occupational studies based on individual data have applied JEMs, especially when individual exposure assessment was impossible. A Finnish JEM (FINJEM) has been developed at the Finnish Institute of Occupational Health (Kauppinen et al., 1998). Three dimensions of FINJEM are job titles, agents, and calendar period. Exposure has been characterized by the proportion of exposed and the mean level of exposure in each job title (Pukkala et al., 2005). Thus, a pancreatic cancer case-control study based on Spanish data (Alguacil et al., 2000a) applied FINJEM. JEMs have been used in several large register-based studies in which exposure assessment at the individual level is not available. Four register-based studies of various cancers (Vasama-Neuvonen et al., 1999; Weiderpass et al., 2003; Guo et al., 2004a; Guo et al., 2004b; Pukkala et al., 2005) applied FINJEM. FINJEM was used also in a pooled study of 11 West European case-control studies of bladder cancer and job titles (Kogevinas et al., 2003), translating job titles to occupational agents at the study level. Hierarchical Bayesian methods and JEM have been applied on individual job title data using logistic regression models in one study (Gilks and Richardson, 1992). Their results from three models, two logistic regression models and one Bayesian logistic regression model, showed that the Bayesian model overestimated results whereas ecological or aggregated bias on average weaken the relative risks.

2.3 Meta-analysis in occupational cancer epidemiology

McElvenny et al. (2004) reviewed meta-analyses of occupational epidemiology. They identified 64 study reports (excluding Studies II and III) published during the period from

1975 to October 2001. Two meta-analyses (Schwartz and Reis, 2000; Wong and Raabe, 2000) were not included. The meta-analysis of Wong and Raabe (2000) was an update of their earlier paper Wong and Raabe (1989). Forty-seven studies had cancer as endpoint. A literature search from October 2001 to December 2005 identified 24 meta-analysis of occupational cancer epidemiology (Sonoda et al., 2001; Wong, 2001; Boffetta, 2002; Gaertner and Thériault, 2002; Levy et al., 2002; Mastrangelo et al., 2002; Boffetta et al., 2003; Crump et al., 2003; Lubin, 2003; Van Maele-Fabry and Willems, 2003; Armstrong et al., 2004; Collins and Lineker, 2004; Goodman et al., 2004; Kurihara and Wada, 2004; Li et al., 2004; Su et al., 2004; Van Maele-Fabry and Willems, 2004; Borak et al., 2005; Bosetti et al., 2005; Buja et al., 2005; Cole and Rodu, 2005; Megdal et al., 2005; Shah et al., 2005; Takkouche et al., 2005).

2.3.1 Characteristics of the meta-analyses

The annual number of meta-analyses of occupational cancer epidemiology has risen during 1981-2005 (Figure 1). Out of the 71 meta-analyses of occupational cancer, twenty applied fixed effects models only. The numbers and proportions of random effects analyses increased during 1981-2005.

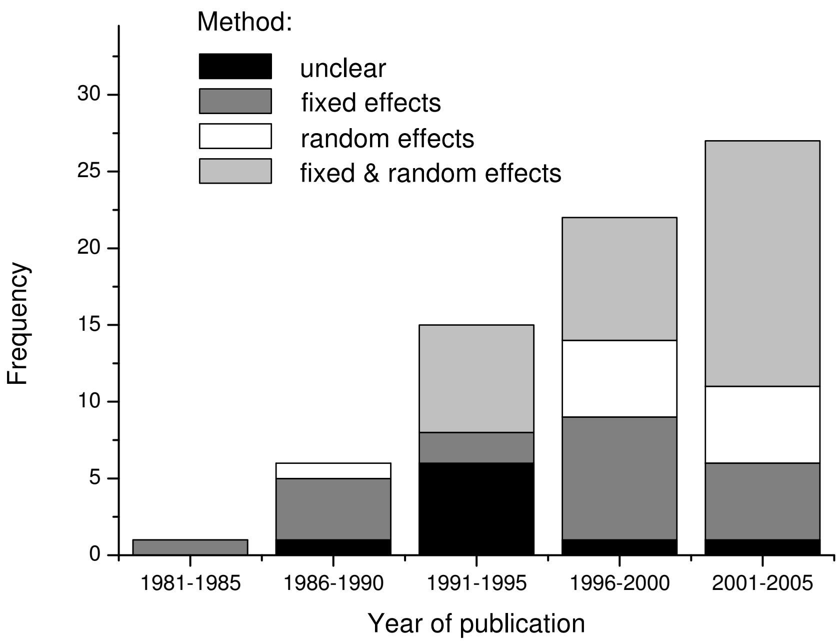


FIGURE 1. Frequency of meta-analyses in occupational cancer epidemiology by publication year and methods of meta-analyses.

Out of 71 meta-analyses of occupational cancer, ten (five job title and five agent specific meta-analyses) reported results for pancreatic cancer (Table 3). One job title study on refinery workers (Wong and Raabe, 2000) is an update of a previous study (Wong and Raabe, 1989). All meta-analyses except one that included various study designs aggregated results of cohort studies. Two job-title specific meta-analyses addressed farmers, and four agent-specific meta-analyses dealt with organic solvents. The number of studies included in meta-analyses ranged from three to 82.

TABLE 3. Characteristics of meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	Job or Agent	No. of studies included	Type of studies included	Fixed/ random effects	Meta parameter
Job title studies:					
Wong and Raabe (1989)	Refinery workers	11	Cohort	Fixed	Meta-SMR
Blair et al. (1992)	Farmers	20	Cohort	Fixed	Meta-SMR
Acquavella et al. (1998)	Farmers	27	Cohort, case-control,	Fixed/ random	Meta-RR
Wong and Raabe (2000)	Refinery workers	25	Cohort	Fixed	Meta-SMR
Greenberg et al. (2001)	Chemical workers	82	Cohort	Fixed/ random	Meta-SMR
Agent studies:					
Shore et al. (1993)	Ethylene oxide	11	Cohort	Fixed/ random	Meta-SMR
Chen and Seaton (1996)	Organic solvents	29	Cohort	Fixed	Meta-SMR
Schwartz and Reis (2000)	Cadmium	3	Cohort	Fixed	Meta-SMR
Wartenberg et al. (2000)	Trichloroethylene	15	Cohort	Fixed	Meta-SMR/ Meta-SIR
Collins et al. (2001)	Formaldehyde	14	Cohort	Fixed/ random	Meta-RR

The type of relative risk estimates was SMR or SIR in all job title specific meta-analyses and mixed (SMR/SIR/OR) in one meta-analysis (Table 4). Only one meta-analysis tested heterogeneity between aggregated studies. Strong associations with any job titles or agents did not be found in any meta-analyses, except for the Acquavella et al. (1998) study that reported a high nonpositive result for farmers.

TABLE 4. The number and the type of the relative risk estimates and the results of the job title specific meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	No. of relative risk estimates	Type of relative risk estimates	Results of meta-analysis: MRR (95% CI)	p-value of heterogeneity
Wong et al. (1989) (refinery workers)	11	SMR	0.95 (0.85-1.05)	Not reported
Blair et al. (1992) (farmers)	20	SMR	0.98 (0.94-1.02)	Not reported
Acquavella et al. (1998) (farmers)				
All studies	28	SMR/PMR/OR	0.94 (0.86-1.02)	<0.00001
Follow-up studies	9	SMR	0.78 (0.74-0.82)	0.15
PMR-studies	11	PMR	1.05 (0.98-1.11)	0.04
Case-control studies	8	OR	1.01 (0.88-1.17)	0.92
Wong and Raabe (2000) (refinery workers)	25	SMR	0.88 (0.82-0.94)	Not reported
Greenberg et al. (2001) (chemical workers)				
All studies	82	SMR	1.00 (0.93-1.08)	Not reported
Male	76	SMR	1.01 (0.93-1.09)	Not reported
Female	14	SMR	0.93 (0.66-1.30)	Not reported
Latency > 10 Years	20	SMR	1.04 (0.85-1.26)	Not reported
Duration > 10 Years	11	SMR	1.13 (0.85-1.51)	Not reported
All studies	9	SIR	1.09 (0.78-1.54)	Not reported

The type of relative risk estimates was SMR or SIR in all agent-specific meta-analyses but one that consolidated mixed estimates (SMR/SIR/PMR/PIR/OR) in one (Table 5). Out of five agents specific meta-analyses four have tested heterogeneity between aggregated studies. Wartenberg et al. (2000) reported a high excess for trichloroethylene in SMR-studies on dry cleaners and laundry operators. Collins et al. (2001) reported a high excess risks for formaldehyde in different study types. For cadmium, Schwartz and Reis (2000) found an MRR 1.66 of a quit strong positive association for men, based on three SMR-studies.

TABLE 5. The number and the type of the relative risk estimates and the results of the agent specific meta-analyses in occupational pancreatic cancer epidemiology published up to December 2005.

Study	No. of relative risk estimates	Type of relative risk estimates	Results of meta-analysis: MRR (95% CI)	p-value of heterogeneity
Shore et al. (1993) (ethylene oxide)				
All studies	8	SMR	0.98 (0.69-1.36)	0.41
Latency (years)				
Brief	3	SMR	1.1 (0.4-2.3)	Not reported
Intermediate	4	SMR	0.8 (0.3-1.6)	Not reported
Long	4	SMR	1.1 (0.6-2.0)	Not reported
Intensity or frequency of exposure:				
Low	3	SMR	0.7 (0.1-2.1)	Not reported
Intermediate	4	SMR	1.0 (0.3-2.3)	Not reported
High	4	SMR	0.9 (0.5-1.5)	Not reported
Duration of exposure				
0-9 y	4	SMR	1.0 (0.5-1.6)	Not reported
> 10y	4	SMR	1.0 (0.5-1.5)	Not reported
Chen and Seaton (1996) (organic solvents)	29	SMR	0.91 (0.84-0.98)	> 0.1
Schwartz and Reis (2000)(cadmium)				
All studies	4	SMR	1.62 (0.94-2.79)	0.73
Male	3	SMR	1.66 (0.98-2.80)	0.89
Wartenberg et al. (2000) (trichloroethylene)				
Tier I (exposure best characterized)	3	SIR	1.2 (0.7-2.0)	Not reported
	4	SMR	0.9 (0.7-1.2)	Not reported
Tier II (exposure putative)	5	SMR	1.1 (0.9-1.3)	Not reported
Tier III (dry cleaner and laundry workers)	2	SIR	1.7 (1.2-2.6)	Not reported
	5	SMR	1.3 (1.0-1.7)	Not reported
Collins et al. (2001)(formaldehyde)				
All studies	14	SIR/SMR/ PMR/PIR/OR	1.1 (1.0-1.2)	0.12
Cohort studies	8	SIR/SMR	1.0 (0.8-1.2)	0.14
PMR/PIR-studies	4	PMR/PIR	1.2 (1.0-1.4)	0.61
Case-control studies	2	OR	1.0 (0.5-2.0)	0.03

2.3.2 Hierarchical Bayesian meta-analysis

In the review of meta-analyses of occupational epidemiology (McElvenny et al., 2004) only one study used Bayesian methods (Biggerstaff et al., 1994). Our literature search from PubMed for period October 2001 to December 2005 did not identify any study of Bayesian meta-analysis of occupational epidemiology. Wraith and Mendersen (2006) recently published a hierarchical Bayesian meta-analysis of lung cancer and interaction with asbestos and smoking.

DuMouchel and Harris (1983) introduced hierarchical models for Bayesian meta-analysis. Recent advances in computational methods have made these methods available for combining the results of epidemiological studies. The fully Bayesian hierarchical model has been investigated extensively by DuMouchel (1990) and Abrams and Sanso (1998) using analytic approximations. Morris and Normand (1992) and Smith et al. (1995) applied sampling-based Markov chain Monte Carlo (MCMC) methods to random effects hierarchical Bayes models for meta-analysis. Carlin (1992) considered meta-analyses of both clinical trials and case-control studies from the Bayesian viewpoint. Biggerstaff et al. (1994) compared classical and Bayesian meta-analyses in studies of lung cancer and passive smoking in workplace. Tweedie et al. (1996) applied Bayesian models to meta-analysis of environmental tobacco smoking and lung cancer studies. DuMouchel (1995) investigated meta-analysis for dose-response models.

3. OBJECTIVES

This study investigated the relationship between occupational determinants and pancreatic cancer.

The specific objectives were:

1. To identify and estimate associations between pancreatic cancer and occupational agents in a case-control study.

2. To extend and estimate the identification of associations between pancreatic cancer and occupational agents in a worldwide meta-analysis, using job title data, a job-exposure matrix, and different methods of meta-analysis.

3. To investigate the applicability of hierarchical Bayesian methods to the occupational meta-analysis data estimating associations between pancreatic cancer and occupational agents indirectly with FINJEM using job titles.

4. MATERIALS AND METHODS

4.1 Case-control study

4.1.1 Materials

In Study I the pancreatic cancer cases and stomach, colon and rectum cancer controls diagnosed in 1984-87 between the ages of 40 and 74 years in Finland and known to be dead by April 1, 1990 were identified at the Finnish Cancer Registry without matching. The study was restricted to the deceased because of the rapid fatality of pancreatic cancer and to reach a reasonable non-differential misclassification of determinant data (surrogate responders for both cases and controls).

A next-of-skin was identified for each case and control from the Finnish Population Registry, and a questionnaire was sent to each. Semi-structured questions requested information on lifetime occupational history of the deceased (branch, job task, employer, and duration of every period of employment); body built (thin/slim/normal/quite fat/fat/unknown); coffee consumption (not at all or irregularly/1-3/4-6/>6 cups per day/unknown); sugar consumption (none/little/moderate/much/unknown); consumption of distilled alcohol (none/moderate/much/unknown), wine, and beer (none/moderate/much/unknown); average daily number of cigarettes smoked (occasionally, little/1-9/10-20/>20 cigarettes per day/unknown) (all the preceding referring to the 1960s); onset of smoking (no/yes/unknown); age at giving up smoking; pancreatitis, diabetes, and biliary stones (no/yes/unknown); and years of diagnosis. Two reminders were mailed to those who did not respond to the initial questionnaire. The persons were encouraged to contact an interviewer by telephone if they felt it would be more convenient.

The response rate for cases was 47%, for stomach cancer controls 53%, for colon cancer controls 47%, and for rectum cancer controls 47%. The criteria for excluding subjects and the numbers of included subjects are in Figure 2. After the exclusions the final number of cases was 595 and that of controls 1,622 (936 stomach cancers, 395 colon cancers, and 291 cancers of the rectum).

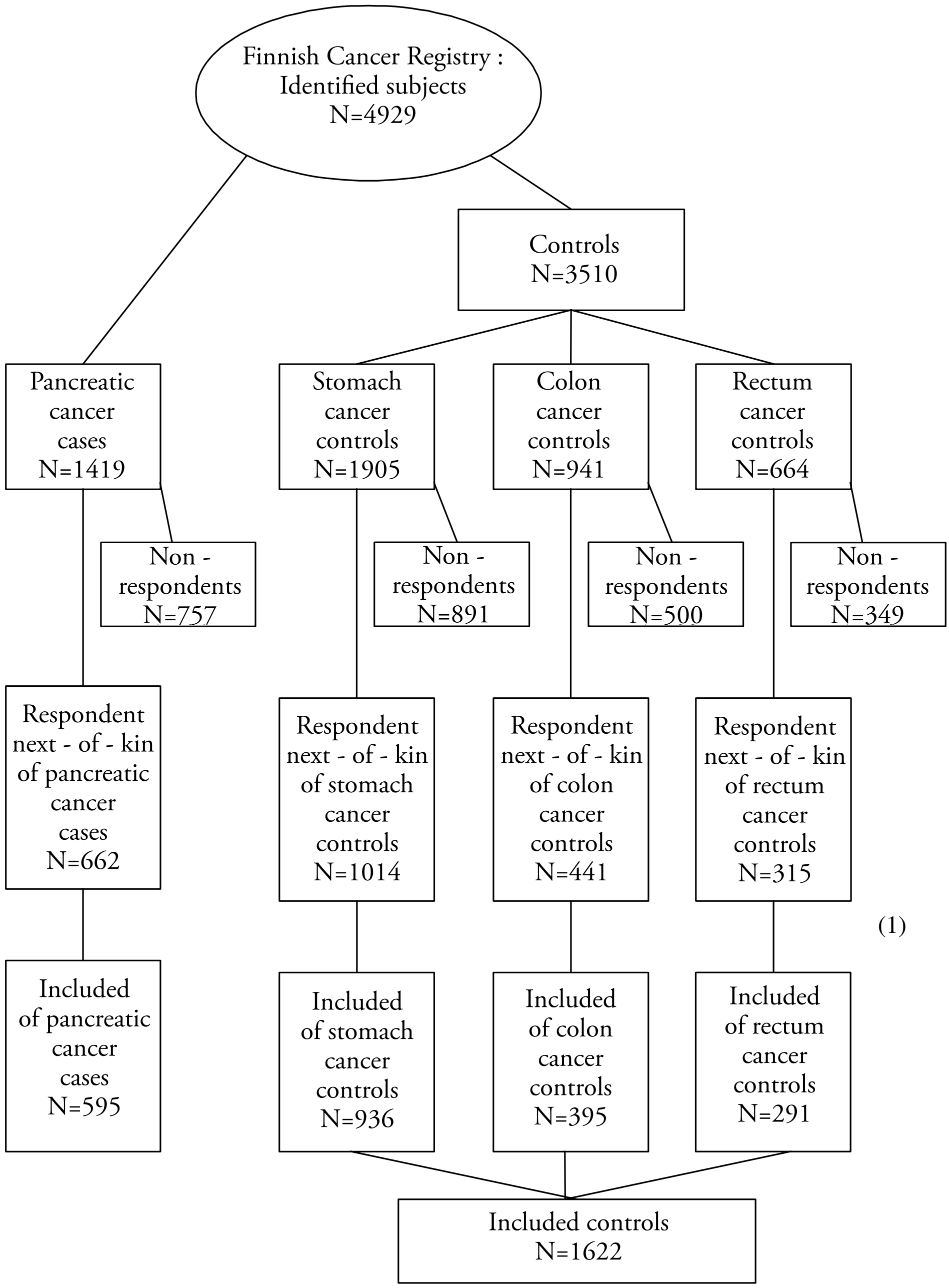


FIGURE 2. Subject ascertainment of the case-control study.
Exclusions (1) endocrine pancreatic cancer cases, subjects with incomplete work histories, subjects with diagnostic pancreatitis before 1982, and administrators and managers.

All reported jobs that lasted at least a year by the end of 1973 (to allow for a minimum lag period of 10 years between the last employment counted and diagnosis) were abstracted from questionnaires and coded by an experienced industrial hygienist according the British Classification of Occupations of General Register Office (HMSO, 1966a) and the Standard Industrial Classification (HMSO, 1966b).

In the agent-specific study (I), the first exposure analysis (industrial hygiene, or "IH" survey) was based on a reconstruction of probable exposure to 17 selected agents: aromatic amines, asbestos, cadmium, chlorophenols, chromium (VI) compounds, engine exhaust, formaldehyde, gasoline, lead, mineral wool, polyaromatic hydrocarbons (PAHs), pesticides, silica, solvents, textile dust, welding, and wood dust. An experienced industrial hygienist determined the criteria for the exposure categories, reviewed the occupational histories, listed the probable agents of the individuals, and rated them by the level of exposure (none/low/high).

The second exposure analysis ("JEM analysis") was a survey of potential agents by a job exposure matrix (JEM). The coded work histories were transformed into exposure indices of 50 chemical agents or other job characteristics with the help of the JEM constructed in Southampton, UK (Pannett et al., 1985). The JEM included from each agents two calendar periods (cutpoint 1950), the probability of exposure (0=none/1=low/2=high), and the level of exposure (0=none/1=low/2=high). Each case and control was assigned to exposure categories defined by the combination of the probability and level of exposure. For example, the assignment to category 2211 for some agent means that the worker is considered to have had a high probability and level of exposure before 1950 and a low probability and level after 1950. To condense the data for the analysis the category with zero probability and zero level before and after 1950 was labeled "no" exposure, high probability and high level before 1950 or/and after 1950 "substantial" exposure, and the remaining exposure categories "low".

A third exposure analysis ("IH reanalysis") was a dose-response analysis of the agents that were associated with excess risk of pancreatic cancer in previous analyses. Two industrial hygienists reclassified all subjects to exposure categories none/light/moderate/heavy. Assignment to heavy category required at least 10 years in high level of exposure, moderate less than 10 years in high level of exposure or at least 10 years in low level of exposure, and light less than 10 years in low level of exposure.

All coding of exposures of the industrial hygienists was done without knowing of the cancer site. Exposures were assessed up until end of 1974 to allow for an induction period of at least 10 years between exposure and end of follow-up (time of diagnosis for the cases).

4.1.2 Statistical methods

Unconditional logistic model was applied using the SAS program. All odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer are adjusted for age (year), gender, smoking in the 1960s (no/yes), total alcohol consumption in the 1960s (five-category ordinal scale), and diabetes (no/yes); and all controls were pooled. Total alcohol consumption was coded as following: zero, if (spirits is none [wine/beer is none or moderate or much or unknown]) or (spirits is unknown and wine/beer is none); one if (spirits is moderate and wine/beer is none); two, if (spirits is moderate and [wine/beer is moderate or much or unknown]) or (spirits is unknown and [wine/beer is moderate or uknown]); three, if (spirits is much and [wine/beer is none or modate or unknown]); four, if (spirits is much and wine/beer is much) or (spirits is unknown and wine/beer is much).

4.2 Meta-analysis

4.2.1 Materials

Study identification and study selection

A literature search of cohort, linkage, proportional, and case-control studies have performed in any language with data on occupations, occupational exposures, and pancreatic cancer in Medline , Toxline, and Cancerlit databases for the period 1969 to May 1998, with the following search conditions:

(1) (occupational OR agriculture) AND neoplasms AND morbidity
(2) (occupational OR agriculture) AND neoplasms AND mortality NOT morbidity
(3) (occupational OR agriculture) AND neoplasms AND incidence NOT mortality NOT morbidity
(4) (pancreatic OR digestive) AND occupational
(5) (pancreatic OR digestive) AND case AND (control OR referent)

Studies from the reference lists of identified studies were also searched.

Data extraction

Appendix 1 shows the standardized data extraction form covering descriptors of the study, relative risk estimates, latency periods, and numbers of exposed cases. Five epidemiologists examined the reports and extracted the necessary data, using predefined rules and selecting the most unbiased estimates; choosing estimates adjusted for at least known risk factors for pancreatic cancer (age, gender, tobacco smoking), preferring social class adjusted relative risks over those unadjusted for social class and choosing relative risk estimates nearest to 20-y latency period. The extracted data were then centrally checked for consistency by two epidemiologists, and finally entered into a database and checked for correctness.

Data analysis

The studies were divided into *(a) agent-specific studies* with direct relative risk estimates for one or several of the 29 agents (Appendix 1), or for job titles with verified exposure(s) to the agent(s), and *(b) job-specific studies* without relative risk estimates for any of the selected agents but instead for one or more of the 150 job categories (Appendix 1), without verified exposure(s) to the agent(s). The agents were based on the Finnish job exposure matrix (FINJEM; Kauppinen et al., 1998). The list of job titles covered 150 entries in the Finnish social status classes 3, 4, and 5. Data for classes 1 and 2 represented the highest social classes and were excluded because the pertinent occupational chemical exposures were minimal or nonexistent. This exclusion may also have eliminated confounding from unknown determinants that may have been prevalent in high social classes.

Missing 95% CIs were recovered with Byar's approximation (Breslow and Day, 1997) in cohort studies, and using approximated estimates of variance of log odds ratio in case-control studies. The data was organized and analyzed by relative risk estimates rather than studies, since there were studies that considered more than one relative risk estimate separately (eg, genders, exposure or job title categories).

From the identified 1,903 studies, a total of 373 studies (112 agent studies and 261 job title studies) remained after the exclusions (Figure 3).

In the meta-analysis of occupational agents (Study II) 162 pancreatic cancer relative risk estimates were reported in 93 agent-specific studies, which represent 23 agents and over 2,836 pancreatic cancer cases. The 23 agents are shown in Table 6. One originally missing relative risk estimate for nickel (Shannon et al., 1991) has been added; see discussion of Seilkop (2001) and Ojajärvi and Partanen (2001).

The meta-analysis for chlorinated hydrocarbon solvents and related compounds (Study III) based on both the agent studies directly addressing exposure to one or several chlorinated hydrocarbon solvents and related compounds and the job title studies addressing to metal plating or dry cleaning, which represent the industries with the highest proportion of workers exposed to chlorinated hydrocarbons and related compounds. Data for chlorinated hydrocarbon solvents included 19 studies, 24 relative risk estimates and over 133 pancreatic cancer cases, and data for the two job titles in 22 studies, 35 relative risk estimates and over 519 pancreatic cancer cases.

The hierarchical Bayesian meta-analysis for job titles and agents (Study IV) was based on the data of 77 job title studies which represent 27 job titles, 151 relative risk estimates and over 3799 pancreatic cancer cases. At an agent data level, FINJEM (Kauppinen et al., 1998) provided proportions of exposed workers for the selected nine occupational agents in 27 job titles (Table 6). For the relative risk estimates of the individual studies, the results were coded into these job categories. The nine were selected because their meta-relative risks in Study II exceeded 1.1.

TABLE 6. Agents included in the meta-analysis of occupational agents (Study III), and of job titles and agents in the hierarchical Bayesian meta-analysis (Study IV).

Agents, Study III:

1. Aliphatic and alicyclic hydrocarbon solvents
2. Aromatic hydrocarbon solvents (excluding aromatic amines)
3. Arsenic
4. Asbestos
5. Cadmium and cadmium compounds
6. Chlorinated hydrocarbon (CHC) solvents and related compounds
7. Chromium and chromium compounds
8. Diesel engine exhaust
9. Electromagnetic fields
10. Flour dust
11. Formaldehyde
12. Fungicides
13. Gasoline
14. Herbicides
15 Insecticides
16. Iron and iron compounds
17. Lead and lead compounds
18. Man-made vitreous fibers
19. Nickel and nickel compounds
20. Oil (including fluid, and cutting fluid)
21. Polycyclic aromatic hydrocarbons (PAH)
22. Silica dust
23. Wood dust

Job titles, Study IV:

1. Asphalt/highway workers
2. Bench carpenters
3. Bricklayers/plasterers/tile setters
4. Cabinetmakers/joiners
5. Concrete mixer operators/ product workers/cement workers
6. Concrete shutterers/finishers
7. Construction carpenters
8. Construction workers unspecified
9. Electric machine operators
10. Farmers
11. Fitters/ assemblers
12. Foundry workers
13. Laundry and dry cleaning workers
14. Machine / engine mechanics
15. Metal plating workers
16. Metal smelting furnacemen
17. Miners/shotfirers/quarry workers
18. Painters/lacquered/floor layers
19. Plywood/fiberboard workers
20. Printers/pressmen/newspaper workers
21. Sawyers
22. Sheet metal workers
23. Smiths
24. Stone cutters
25. Timbermen/lumbermen
26. Turners/toolmakers/machine-tool setters
27. Wood working machine operators.

Agents, Study IV:

1. Aliphatic and alicyclic hydrocarbon solvents (ALHC)
2. Chlorinated hydrocarbon compounds (CHC)
3. Chromium and chromium compounds (CR)
4. Fungicides (FUNG)
5. Insecticides (INSC)
6. Nickel and nickel compounds (NI)
7. Polycyclic aromatic hydrocarbons (PAH)
8. Silica dust (SIL)
9. Wood dust (WOOD).

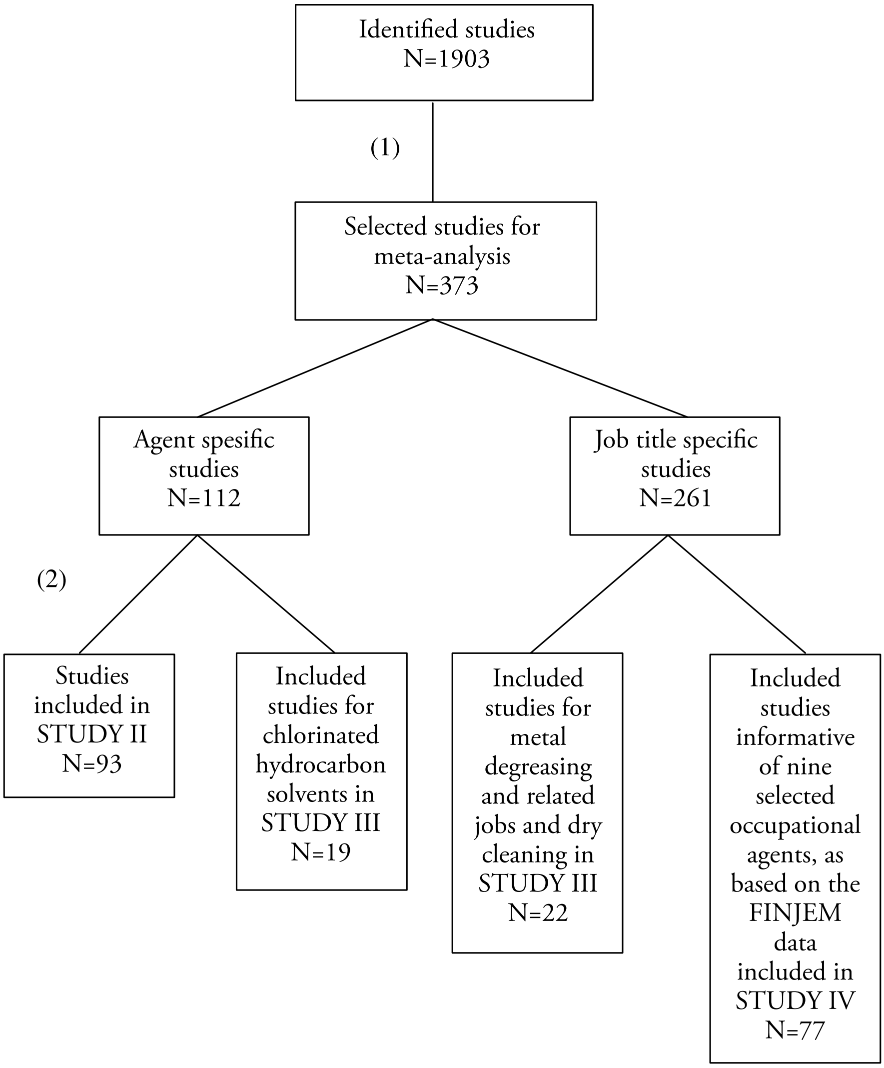


FIGURE 3. Flow diagram of the meta study

(1) Excluded: studies that did not report on pancreatic cancer; did not represent the most recent update; reported insufficient data for the meta-analysis; did not report data for any job or occupational agent; did not report original results (reviews); reported on part of a larger population reported elsewhere; or reported on job categories or agent categories too broad or outside our list of job titles and agents.

(2) Excluded all (10) ionizing radiation, radon and nine insecticide studies.

4.2.2 Statistical methods

Meta-analysis of non-experimental data

Meta-analysis is a statistical analysis which combines the results of several independent studies. This is a meta-analysis of non-experimental studies.

TABLE 7. The notation used in the meta-analytic models

i	index of relative risk estimates
j	index of parameters
M	number of relative risk estimates
N	number of parameters
RR_i	observed estimate of relative risk for relative risk estimate i
RR_{Li}	95% lower confidence limit of RR_i
RR_{Ui}	95% upper confidence limit of RR_i
y_i	observed $\ln(RR_i)$ of relative risk estimate i
θ_i	true $\ln(RR_i)$ of relative risk estimate i
s_i^2	variance of $\ln(RR_i)$ for relative risk estimates i
σ_θ^2	between-risk-estimates variance
x_{ij}	element of MxN relative risk estimate parameter matrix
β_j	mean of $\ln(RR_i)$ for parameter j

The formula of meta-analysis model is

$$
\begin{aligned}
(1) \qquad & y_i = \theta_i + e_i \\
& \theta_i = \Sigma_j x_{ij} \beta_j + \varepsilon_i \\
& e_i \sim \text{Normal}\ (0, s_i^2) \\
& \varepsilon_i \sim \text{Normal}\ (0, \sigma_\theta^2),
\end{aligned}
$$

where $s_i^2 = \ln(RR_{Li} / RR_{Ui}) / 3.92$. If number of parameters N and x_{ij} are 1's and $\sigma_\theta^2 = 0$ in the formula (1) indicating homogeneity between observed risk estimators, then the meta-analysis model is *a simple fixed effects model*, and if $\sigma_\theta^2 > 0$ then the model is *a simple random effects model.* If $N > 0$ and $\sigma_\theta^2 = 0$, the model is *a fixed effects meta-regression model*, and if $N > 0$ and $\sigma_\theta^2 > 0$, the model is *a random effects meta-regression model*. Random effects models for meta-analysis are 2-level hierarchical models.

Making distributional assumptions for β_j and σ_θ^2

(2) $\beta_j \sim p(\beta_j)$
$\sigma_\theta^2 \sim p(\sigma_\theta^2)$,

the model is a hierarchical Bayesian (HB) model for meta-analysis.

Bayesian theory and Markov chain Monte Carlo technique

Let $\boldsymbol{Y}$ denote the observed data and $\boldsymbol{\psi}$ unknown parameters. Bayes's theorem is

$$p(\boldsymbol{\psi}|\boldsymbol{Y}) = \frac{p(\boldsymbol{Y}|\boldsymbol{\psi})\,p(\boldsymbol{\psi})}{p(\boldsymbol{Y})},$$

where the conditional probability distribution of $\boldsymbol{\psi}$ given $\boldsymbol{Y}$, $p(\boldsymbol{\psi}|\boldsymbol{Y})$, is called the posterior probability distribution, $p(\boldsymbol{Y}|\boldsymbol{\psi})$ is the likelihood, $p(\boldsymbol{\psi})$ is the prior probability distribution, and the denominator is a normalizing constant (Gelman et al., 2003).

In Bayesian inference, there are possible point estimators for $\boldsymbol{\psi}$, namely, a posterior mean, a posterior median and a posterior mode. In Bayesian statistics, a posterior probability interval is called a credible interval (CrI) which is Bayesian analogue of a frequentist confidence interval (CI).

A Markov chain Monte Carlo (MCMC) algorithm is known as Gibbs sampling. MCMC methods are numerically approximated by constructing chains by starting different initial values by Gibbs sampling (Gilks et al., 1996) and simulating the chains. The convergences of the chains can be assessed by examining Monte-Carlo errors and Gelman-Rubin statistics (Brooks and Gelman, 1998).

Let R denote the number of draws $\boldsymbol{\psi}^{(1)}, \boldsymbol{\psi}^{(2)},\ldots, \boldsymbol{\psi}^{(R)}$. Let the parameter be $\boldsymbol{\psi} = (\psi_1, \psi_2,\ldots, \psi_s)$. Initializing the MCMC method, the parameter $\boldsymbol{\psi}$ gets any convenient starting value $\boldsymbol{\psi}^{(0)}$. After performing so called burn-in of T iterations, the parameter $\boldsymbol{\psi}^{(t)}$ has approximately the chain's limiting distribution, where $t = T+1, T+2,\ldots,T+M$. The length of the burn in T depends on the starting value $\boldsymbol{\psi}^{(0)}$ and the convergerence of the parameter $\boldsymbol{\psi}$. The convergerence of the parameter $\boldsymbol{\psi}$ can be checked graphically in single-chain methods, and statistically in multi-chain methods such as a Monte Carlo error and Gelman-Rubin statistics (Brooks and Gelman, 1998). The Gibbs sampler starts with an initial value, and the convergerence of the parameter $\boldsymbol{\psi}^{(0)}$ has the following iterative procedure:

Draw $\psi_1^{(1)}$ from $p(\psi_1 \mid \psi_2^{(0)}, \psi_3^{(0)},\ldots,\psi_s^{(0)}, \boldsymbol{Y})$
Draw $\psi_2^{(1)}$ from $p(\psi_2 \mid \psi_1^{(1)}, \psi_3^{(0)},\ldots,\psi_s^{(0)}, \boldsymbol{Y})$
.
.
.
Draw $\psi_s^{(1)}$ from $p(\psi_s \mid \psi_1^{(1)}, \psi_2^{(1)},\ldots,\psi_{s-1}^{(1)}, \boldsymbol{Y})$
Draw $\psi_1^{(2)}$ from $p(\psi_1 \mid \psi_2^{(1)}, \psi_3^{(1)},\ldots,\psi_s^{(1)}, \boldsymbol{Y})$
.
.
.
and so on.

After each iteration there are new values for all elements of $\boldsymbol{\psi}$. One iteration consists of s draws from one-dimensional full conditional distribution. A unique limiting distribution for the Gibbs sampler is a full joint posterior distribution $p(\boldsymbol{\psi} \mid \boldsymbol{Y})$.

Applications of meta-analysis for occupational data

In the agent specific meta-analysis (Study II) and in the meta-analysis for chlorinated hydrocarbon solvents and related compounds (Study III), simple random effects (RE) models were applied for estimating the meta relative risks (MRRs), implying that σ_θ^2 is greater than zero in formula (1), and the weight of population i is $1/(s_i^2+\sigma_\theta^2)$. The between-risk-estimate variance σ_θ^2 was estimated using the method proposed by DerSimonian and Laird (1986). In Study III for trichloroethylene and methylene chloride data, random effects linear meta-regression models were applied for log relative risk, implying that x_{ij} is a dose in formula (1).

Study IV is a first application of hierarchical Bayesian methods of meta-analysis on published epidemiological studies that associated the risk of pancreatic cancer with occupations, using higher-level data for occupational agents. Two different hierarchical Bayesian models for job titles (lower-level) and occupational agents (higher-level) were used. Non-Bayesian simple random effects models for job titles were also applied to check consistency with Bayesian results. A Finnish job-exposure matrix (FINJEM) provided the higher-level data (Kauppinen et al., 1998). This is a hierarchical Bayesian meta-analysis of occupations and pancreatic cancer based on studies that addressed to job title studies.

In the HB models let $i = 1,\ldots,M$ denotes the index of relative risk estimates from studies. Let $j = 1,\ldots,N$, $k = 1,\ldots,O$, and $l=1,\ldots,P$ denote the index of job titles, covariates, and agents, respectively. The number of relative risk estimates (M) was 151, the number of job titles (N) 27, the number of covariates (O) five, and the number of occupational agents (P) eight.

In the HB models x_{ij} is the element of relative risk estimates-job MxN-matrix with the value of unity when relative risk estimates (RR_i and s_i) were available for job j and zero otherwise; w_{ik} is the element of relative risk estimates-covariate MxO-matrix of 1:s and 0:s; and z_{jl} is s element of the job-exposure NxP-matrix which comes from FINJEM. The relative risk estimate-covariate matrix included five dichotomized covariates: study type (case-control vs. cohort), publication year (cutpoint 1990), diagnosis of pancreatic cancer (histological vs. other), country (Denmark, Finland, Norway and Sweden vs. others) and time reference for job title (longitudinal vs. other). Appendix 2 shows job-exposure matrix used in the hierarchical Bayesian models where z_{jl} is the element of job-exposure NxP-matrix, i.e., the proportion of exposed, as provided by FINJEM if over 20% of the workers in job category j were exposed to agent l on the period 1960-85 and zero otherwise.

Let β_j denote the parameter of job j representing the mean log of relative risks for job j for all studies combined and σ_β^2 the variance of parameter β_j. Let γ_k denote the mean log of relative risks for covariate k for all studies combined, and μ_γ and σ_γ^2 its mean and variance, respectively. Let π_l denote the mean log of relative risks for agent l for all studies combined and μ_π and σ_π^2 its mean and variance, respectively. Let Normal(μ, σ^2) denote the normal distribution with mean μ and variance σ^2. Let Gamma(a, b) denote the gamma distribution with mean a/b and variance a/b^2.

The hierarchical Bayesian method of meta-analysis for job titles and occupational agents there were following distributional assumptions:

$$
\begin{aligned}
(3)\qquad & y_i \sim \text{Normal}(\theta_i\,,\, s_i^2), && i=1,\ldots,M\\
& \theta_i \sim \text{Normal}(\Sigma_j\, x_{ij}\beta_j + \Sigma_k\, w_{ik}\gamma_k\,,\, \sigma_\theta^2), && i=1,\ldots,M;\ j=1,\ldots,N;\ k=1,\ldots,O\\
& \beta_j \sim \text{Normal}(\Sigma_l\, z_{jl}\pi_l,\ \sigma_\beta^2), && j=1,\ldots N;\ l=1,\ldots,P
\end{aligned}
$$

and prior normal distributions for γ_k and π_l

$$
\begin{aligned}
(4)\qquad & \gamma_k \sim \text{Normal}(\mu_\gamma\,,\, \sigma_\gamma^2) && k=1,\ldots,O\\
& \pi_l \sim \text{Normal}(\mu_\pi\,,\, \sigma_\pi^2), && l=1,\ldots,P
\end{aligned}
$$

and prior gamma distributions to the precisions $1/\sigma_\theta^2$ and $1/\sigma_{\beta j}^{\;2}$

$$
\begin{aligned}
(5)\qquad & 1/\sigma_\theta^2 \sim \text{Gamma}(a,\, b) &&\\
& 1/\sigma_{\beta j}^{\;2} \sim \text{Gamma}(c,\, d) && j=1,\ldots,N
\end{aligned}
$$

Figure 4 shows the directed acyclic graph (DAG), which represents equations (3)-(5). In the DAG single boundary squares contain observed data (relative risk estimates, job titles, and covariates from observed data and agents from FINJEM data). The circles represent unknown and must be estimated. The double squares are fixed parameters of prior distributions. The full arrows represent stochastic relationships and the dashed arrows functional relationships. The shaded nodes are normally distributed and these distributions are represented in the equations (3) and (4) and the non shaded circle nodes are gamma distributed with fixed parameters in the equation (5).

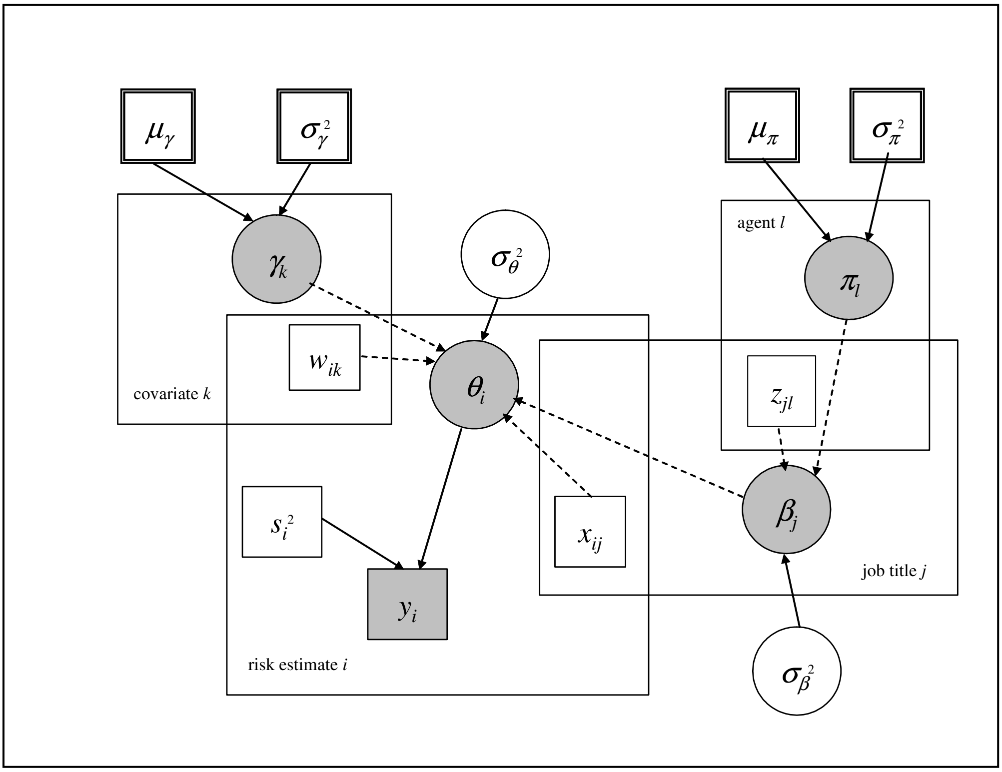


FIGURE 4. A directed acyclic graft for applying hierarchical Bayesian meta-analysis with data from FINJEM.

In both HB models the fixed parameters of prior distributions assumed to be followings: $\mu_\gamma = \mu_\gamma = 0$ and $\sigma_\gamma^2 = \sigma_\pi^2 = 1$. The following assumptions were made for gamma distributions in equation (5):

- HB model 1: $a = b = c = d = 0.1$ meaning that the priors for the precisions are diffuse (Congdon, 2003)
- HB model 2: $a = c = 0.001$ and $b = d = 1$ meaning that the priors for precisions are quite diffuse or reasonable (Congdon, 2003; Wakefield, 2004).

A test of heterogeneity between studies was performed as a χ^2 –test with degrees of freedom less than the number of observed relative risk estimates for each agents in Study II and III, and for each job titles in Studies III and IV. Both the Egger's regression asymmetry test (Egger et al., 1997) and the Begg's adjusted rank correlation test (Begg and Mazumdar, 1994) were used to formally test publication bias in all meta-analyses. The statistical software package Stata 8 for Windows was used (Sharp and Stern 1997) in all simple random effects models for meta-analysis and random effects meta-regression models. In Study IV the MCMC methods constructing two chains starting different initial values by Gibbs sampling (Gilks et al., 1996). Chains were simulated by using the WinBUGS software (Spiegelhalter et al., 1999). The convergences of the chains were assessed by examining Monte-Carlo errors and Gelman-Rubin statistics (Brooks and Gelman, 1998). The WinBUGS program version 1.3 being freely available from http://www.mrc-bsu.cam.ac.uk/bugs was used in the hierarchical Bayesian models.

In the meta-analysis, the random-effects meta-estimates for job titles (Studies III and IV) and agents (Studies II and III) are calculated without covariates. In Study IV, the hierarchical Bayesian models for meta-analysis included five covariates (study type, publication year, diagnosis of pancreatic cancer, country, and time reference for job title). Antilogs of posterior medians were calculated as MRRs in Study IV, since the posterior median is preferable over posterior mean in preserving the antilog transformation.

5. RESULTS

5.1 Background data

5.1.1 Case-control study

Table 8 describes the distribution of a number of background factors and potential confounders. The distributions of gender, age, obesity, and sugar consumption were very similar between the cases and the controls. The main differences were found in the higher proportion of cases consuming substantial alcohol, smoking over 20 cigarettes/day, and having history of biliary stones, diabetes, and pancreatitis.

TABLE 8. Distribution of some background factors between cases and controls in Study I.

Factor	Cases	Controls
Gender (men) %	61	62
Birth year: Mean (SD)	1922 (8)	1921 (8)
Obesity in 1960s (rather fat or fat) %	23	22
Coffee consumption in 1960s (over 6 cups/day) %	18	20
Sugar consumption (much in 1960s) %	13	13
Spirits (much in 1960s) %	8	6
Wine/beer (much in 1960s) %	8	4
Smoking (yes in 1960s) %	57	44
Smoking (over 20 cigarettes/d in 1960s) %	13	9
Biliary stones (ever) %	18	14
Diabetes (ever) %	13	10
Pacreatitis (diagnosed after 1982, ever) %	2	1

5.1.2 Meta-analyses

In the meta-analyses, most observed relative risk estimates (in total 164 in Studies II and IV) were from Europe, closely followed by North America (135 relative risk estimates; Table 9). There were few studies from Central and Eastern Europe, Oceania and Asia, and none from Middle and South America or Africa. The annual number of studies was rising considerably during 1969-1998 (nine relative risk estimates during 1969-79 in Studies II and III; 98 relative risk estimates during 1980-89, and 206 relative risk estimates during 1990-98)

The agent specific meta-analyses (Study II) included predominantly industrial cohort studies (89 observed relative risk estimates), while the bulk of job title studies in Study VI were record linkage studies entirely based on linkage of extraneous databases on job titles (eg, census) and on outcomes (eg, death records; Table 10). Most studies addressed men; only 7% of observed relative risk estimates were for women. The cases represented all pancreatic cancers, irrespective of type. As most studies considered mortality, the diagnosis was in most observed relative risk estimates obtained from the death record. Exposure assessment was longitudinal for 128 relative risk estimates in Study II; job assessment was longitudinal for 107 relative risk estimates in Study IV.

TABLE 9. Distribution of observed relative risk estimates studied in Studies II-IV by location and publication year. Numbers are observed relative risk estimates.

	Study II	**Study III**		**Study IV**
		Agent	Job title	
LOCATION				
Denmark	2	-	5	10
Finland	17	1	2	23
Iceland	-	-	-	1
Norway	3	-	-	4
Sweden	7	1	1	18
Nordic	3	1	-	-
France	1	-	-	6
The Netherlands	2	-	-	2
U.K.	18	3	2	10
Czech Republic	-	-	-	1
Germany	3	-	-	2
Switzerland	-	-	-	4
Italy	10	-	-	14
Poland	1	-	-	-
USSR/Russia	1	1	-	-
Canada	23	3	2	3
U.S.A.	63	13	20	44
Canada and U.S.A.	-	-	-	1
Japan	3	1	3	3
Australia	1	-	-	1
New Zealand	-	-	-	2
U.K. and U.S.A.	-	-	-	2
Multiple countries	3	-	-	-
PUBLICATION YEAR				
1969-1979	2	-	-	7
1980-1989	58	8	19	40
1990-1998	102	16	16	104
TOTAL	**162***	**24**	**35**	**151**

* One study added (Shannon et al. 1991)

TABLE 10. Characterization of the meta-analysis studies (Studies II-IV). Numbers are observed relative risk estimates, OR=odds ratio, SIR=standardized incidence ratio, SMR=standardized mortality ratio, HR=hazard ratio, RR=risk ratio, MOR=mortality odds ratio, PMR=proportional mortality ratio, and PCMR= proportional cancer mortality ratio.

	Study II	**Study III**		**Study IV**
		Agent	Job title	
Study type				
Record linkage	23	4	23	69
Industry cohort	89	16	8	67
Industry based (nested) case-control	7	1	-	-
Population or hospital based case-control	43	3	4	15
Gender				
Men	113	17	22	116
Women	8	4	9	13
Both gender or unspecified	41	3	4	22
Cases				
Exocrine pancreatic cancer only	32	4	-	5
All pancreatic cancers	128	19	32	135
Unspecified	2	1	3	11
Diagnosis of cases				
Histological	47	4	5	27
Other (clinical: radiology, necropsy, etc)	2	1	-	1
Mortality files	97	18	26	79
Mixed	9	-	-	21
Unknown	7	1	4	23
Ascertainment of case				
Mortality files	99	19	27	77
Cancer registry files	40	3	7	57
Hospital regards	21	2	-	7
Mixed	1	-	1	9
Unknown	1	-	-	1
Risk measure				
OR	50	3	1	15
SIR	17	3	4	54
SMR	70	13	6	69
HR	3	-	-	-
RR	4	1	3	23
MOR	-	-	3	-
PMR	18	4	14	-
PCMR	-	-	4	-
Time reference for exposure/job title				
Last or around diagnosis	17	2	3	8
Earlier cross-section	9	-	6	28
Lifetime longitudinal	47	2	-	4
Less than lifetime longitudinal	81	16	22	103
Other	1	1	-	-
Unknown	7	3	6	8
TOTAL	162*	24	35	151

* One study added (Shannon et al. 1991)

5.2 Results of occupational determinants

5.2.1 Occupations

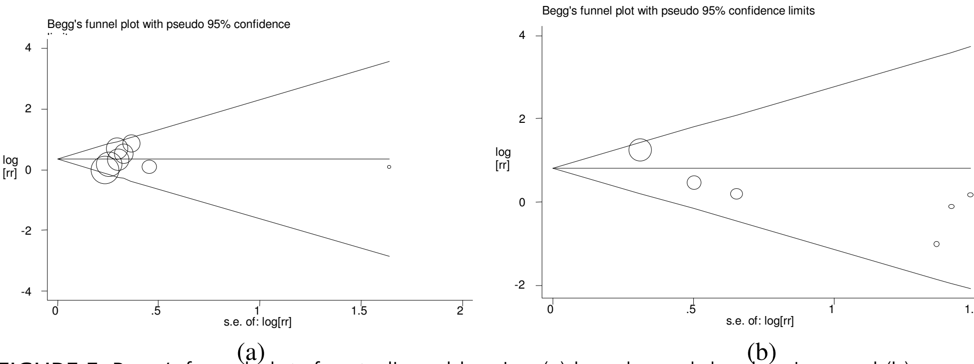
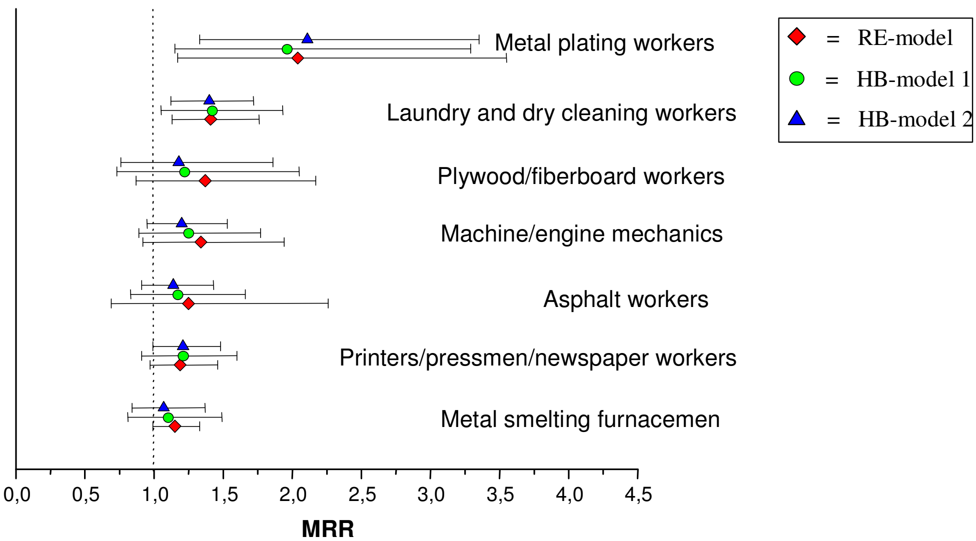


FIGURE 5. Begg's funnel plots for studies addressing (a) laundry and dry cleaning, and (b) metal plating workers: The sizes of graphic symbols representing the data are proportional to the inverse variance. Log[rr] is natural logarithm of relative risk and s.e. of log[rr] standard error of natural logarithm of relative risk.

In Study IV, an evidence of heterogeneity in the relative risk estimates was found for studies addressing to asphalt workers, farmers, painters, and sawyers. Between-study heterogeneity was addressed by using random effects model. Testing publication bias with Begg's and Egger's test it was suspected only for studies addressing metal plating workers. Figure 5 shows Begg's funnel plot studies addressing (a) laundry and dry cleaning, and (b) metal plating workers. In the Figure 5 (b), there is an evidence of publication bias, while the other (a) appears unbiased.



(a)

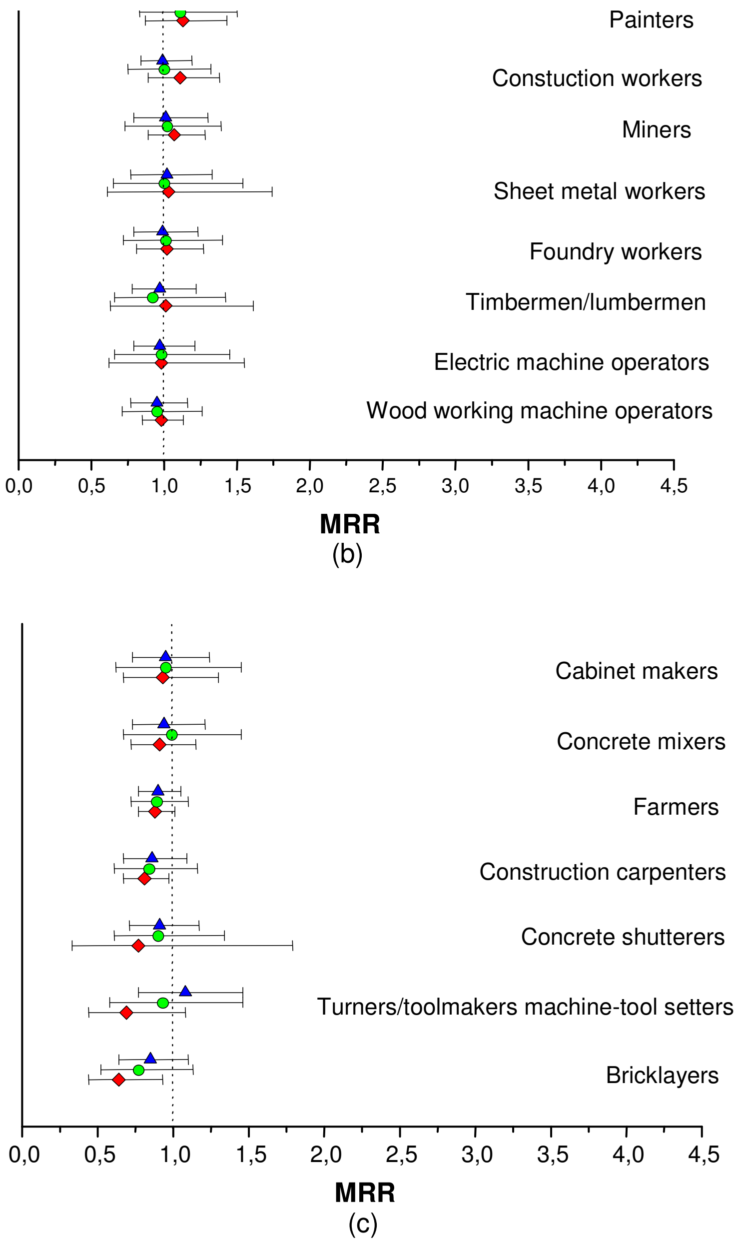


FIGURE 6. Results of 22 job titles from random effects (RE) and hierarchical Bayesian (HB) models for meta-analysis (MRR, meta relative risk, antilog of median).

In Study IV, the MRRs exceeded unity for 12 out of the total of 27 job titles in all meta-analyses, including the non-Bayesian and Bayesian models. In the RE models, MRRs exceeded unity in 16 job titles. For three job titles (metal plating workers, laundry and dry cleaning operators, and printers/pressmen/newspaper workers), MRRs were higher in one or the other of the two HB models. The remaining 11 job titles had MRRs <1 in the RE models. The MRRs were smaller in the HB models than in the RE model for wood working machine operators only.

The results of 22 job titles including more than one observed relative risk estimate are shown in Figure 6 where job titles with highest MRRs are in section (a) and lowest in section (b). The highest MRRs were found for studies addressing metal plating workers in HB model 2 (MRR 2.1, 95% CrI 1.3-3.4), in HB model 1 (MRR 2.0, 95% CrI 1.2-3.2), and in RE model (MRR 2.0, 95% CI 1.2-3.6), based on one OR, three SIR/SMR, and one RR estimates. The second highest excesses were found for studies on laundry and dry cleaning workers in HB model 1 (MRR 1.4, CrI 1.1-1.9), in HB model 2 (MRR 1.4, 95 %CrI 1.1-1.8), and in RE model (MRR 1.4, 95% CI 1.1-1.8); seven SIR/SMR relative risk estimates. A decreased risk was found for bricklayers in RE model (MRR 0.6, 95% CI 0.4-0.9), in HB model 1 (MRR 0.8, 95% CrI 0.5-1.1), and in HB model 2 (MRR 0.9, 95% CrI 0.6-1.1).

5.2.2 Occupational agents

Table 11 presents selected results of occupational agents of the case-control study (Study I) and the meta-analysis (Studies II-IV). No strong associations with results for particular agents were shared by the case-control study and in the meta-analysis.

Case-control study

The highest excess risks for pancreatic cancer were found for exposure to aliphatic and alicyclic hydrocarbons (OR 1.6, 95% CI 1.0-2.6) and aromatic hydrocarbons (1.8, 1.1-2.8) in the IH reanalysis; ionizing radiation (4.3, 1.6-11) in the JEM analysis; and inorganic mineral dust in both the IH survey (2.0, 1.2-3.5) and in the JEM analyses (2.6, 1.5-4.8). In the IH survey an excess risk was found for high exposure to organic solvents (2.0, 1.0-4.1) and to pesticides (1.6, 0.8-3.4). Using colon cancer controls in the IH survey an excess risk for exposure to pesticides was higher (4.8, 1.1-22). Excesses over OR>1.3 and lower 95% CI>0.9 were found for acrylonitrile, chromium and high temperature on the JEM analysis. A strong negative association between pancreatic cancer and exposure to asbestos was found in the IH-survey analysis.

The corrected results for all solvents in IH survey analysis (Table 2 in Study I) are OR 1.38, 95% CI 0.89-2.13, with number of exposed cases 34.

Meta-analysis

In Study II an evidence of heterogeneity in the estimates of relative risks across studies was found for studies addressing asbestos, electromagnetic fields, chlorinated hydrocarbon compounds, and man-made vitreous fibers. Between-study heterogeneity was addressed by using random effects model. Testing publication bias with Begg's and Egger's tests studies did not suggest publication bias for any agent.

Observed relative risk estimates and results by occupational agents and study types from Study II are shown in Appendix 3. In Study II, the highest excesses were found for chlorinated hydrocarbon compounds in the RE model (MRR 1.4, 95% CI 1.0-1.8; 20 relative risk estimates) and for nickel and nickel compounds (MRR 1.7; 95% CI 1.1- 2.5; five relative risk estimates; re-estimated including results of Shannon et al., 1991). For nickel the MRR was highest for case-control studies (MRR 2.0, 95% CI 1.2-3.2; two relative risk estimates: Appendix 3). In Study IV, excesses were found for chlorinated hydrocarbon compounds in HB model 1 (MRR 2.0, 95% CrI 1.0-4.1) and in HB model 2 (MRR 2.2, CrI 1.3-3.7), but the MRRs for nickel were only 1.0 and 1.2 in HB models 1 and 2, respectively. The MRRs and 95% CrIs for insecticides were in HB models 1 and 2 (MRR 1.5; 95% CrI 0.3-7.1) and (MRR2.0, 95% CrI 0.5-7.4), respectively, and the result of the RE model was (MRR 1.5; 95% CI 0.6-3.7; three relative risk estimates).

In Study II, a high excess risk was found for SIR/SMR studies on asbestos (MRR 1.2, 95%CI 1.0-1.5; 20 relative risk estimates), whereas the case-control studies resulted in an MRR of 0.7 (95% CI 0.5-1.0; four relative risk estimates). An excess was found also for SIR/SMR studies for chromium and chromium compounds (MRR 2.3, 95% CI 0.9-5.8; six relative risk estimates) and for OR studies the MRR was 1.0 and 95% CI 0.7-2.0 based on three relative risk estimates. In the Study IV, the MRRs for chromium were 1.0 and 1.1 in the HB model 1 and 2, respectively.

TABLE 11. Results of occupational agents for the case-control study and the meta-analysis study.

AGENT OR* (95% CI*)	Case-control study: Study I MRR* (95% CI)	Meta-analysis study: Random effects models: Study II MRR (95% CI)	Study III MRR (95% CrI*)	Hierarchical Bayesian models: Study IV Model 1 MRR (95% CrI)	Model
Organic solvents	JEM* 1.3 (0.9-2.0)	-	-	-	-
Acrylonitrile	JEM: 2.1 (0.9-4.7)	-	-		
Aliphatic alicyclic hydrocarbons	IH*: 1.6 (1.0-2.6)	1.3 (0.8-2.0)	-	1.1 (0.7-1.9)	1.1 (0.8-1.5)
Aromatic hydrocarbons	IH: 1.8 (1.1-2.8)	1.3 (0.9-1.7)†	-	-	-
Chlorinated hydrocarbons	IH: 1.1 (0.5-2.6)	1.4 (1.0-1.8)	-	2.0 (1.0-4.1)	2.2 (1.3-3.7)
Trichloroethylene	-	-	1.2 (0.8-2.0)	-	-
Methylene chloride	-	-	1.4 (0.8-2.5)	-	-
Vinyl chloride	-	-	1.2 (0.7-1.9)	-	-
Polychlorinated biphenyls	-	-	1.4 (0.6-3.3)	-	-
Other organic solvents	IH: 1.6 (0.9-6.0)	-	-	-	-
Organic dust	JEM: 1.0 (0.8-1.3)	-	-	-	-
Wood dust	IH: 1.3 (0.8-2.1)	1.2 (0.9-1.6)	-	1.0 (0.7-1.3)	1.0 (0.8-1.2)
Inorganic mineral dust	IH: 2.0 (1.2-3.5)	-	-	-	-
Asbestos	IH: 0.6 (0.4-0.9)	1.2 (1.0-1.5)§	-		
Silica dust	-	1.4 (0.9-2.0)	-	0.9 (0.7-1.2)	0.9 (0.7-1.1)
Metals					
Chromium	IH: 0.9 (0.4-2.0)	2.3 (0.9-5.8)§		1.0 (0.5-2.3)††	1.1 (0.6-1.8)††
Lead	JEM: 1.4 (0.9-2.1)	1.1 (0.8-1.5)	-	-	-
Nickel	-	1.7 (1.1-2.5)#	-	1.0 (0.5-2.3)††	1.1 (0.6-1.8)††
Arsenic	JEM: 1.2 (0.9-1.8)	1.2 (0.5-2.6)**	-	-	-
Engine exhaust					
Polycyclic aromatic hydrocarbons	IH: 1.3 (0.7-2.6)	1.5 (0.9-2.4)	-	1.1 (0.8-1.6)	1.1 (0.9-1.5)
Pesticides	IH: 1.7 (0.8-3.4)	-	-	-	-
Fungicides	IH 1.4 (0.7-7.2)	1.3 (0.4-3.8)	-	1.1 (0.4-3.2)	0.9 (0.5-1.9)
Insecticides	-	1.5 (0.6-3.7)	-	1.5 (0.3-7-1)	2.0 (0.5-7.4)
Herbicides	JEM: 1.0 (0.8-1.2)	1.1 (0.8-1.5)§	-	-	-
Physical agents					
Ionizing radiation	JEM: 4.3 (1.6-11)	-	-	-	-
Ultraviolet light	JEM: 1.2 (0.8-1.9)	-	-	-	-

- Not estimated. * OR, odds ratio; CI, confidence interval; MRR, meta relative risk; CrI, credible interval JEM, job exposure matrix; IH, industrial hygiene expert assessment of exposures. † Estimate for both genders. § For cohort studies. # Re-estimated including results of Shannon et al. (1991).
** For case-control studies. †† Nickel and chromium

6. DISCUSSION

In this study, excess risk of pancreatic cancer was confined to a small number of job titles, including metal plating workers, laundry and dry cleaning, plywood/fiberboard workers, machine/engine mechanics, asphalt workers printers/pressmen/newspaper workers, metal smelting furnacemen, and painters. These excesses were seen in all non-Bayesian and Bayesian meta-analyses. Heavy exposure to organic solvents and pesticides were consistently associated with pancreatic cancer. In addition, the non- Bayesian meta-analysis showed evidences of excess risks for occupational exposure to chlorinated hydrocarbon solvents and related compounds, and nickel and nickel compounds. The Bayesian meta-analysis for occupational exposure showed high excess risks to chlorinated hydrocarbon solvents and insecticides, but not for nickel. In Study II, there were only five studies addressing to nickel and all found an excess risk for pancreatic cancer. Workers exposing to nickel are exposed often also to other occupational agents such as chromium and chlorinated hydrocarbon solvents.

It appears that either environmental factors play a small etiologic role in the development of pancreatic cancer, or the involvement of yet unknown factors is high, or both. In addition, interactions between environmental and endogenous factors may be important in the etiology of pancreatic cancer.

6.1 Material and methods

The histological diagnosis of pancreatic cancer improves specificity and sensitivity (Engel et al. 1980; Mack, 1982). In addition to refinement of exposure assessment, endpoint delineation requires serious attention in pancreatic cancer epidemiology. Variations in diagnostic practices may obscure interpretations of differences in pancreatic cancer risk between populations and time periods. Of the histologically confirmed pancreatic cancer cases, 29 % may in fact not have originated in the pancreas (Lyon et al., 1989). Such misclassification rates induce biases in risk estimates for etiologic factors (Porta et al., 1994). For example, Garabrandt et al. (1993) compared, in a case-control study of pancreatic cancer, ORs for DDT family between cases representing death certificates and cases representing cytohistological verification. For death certificate cases the ORs ranged from 0.8 to 2.6 and for cytohistologically verified cases, from 15.4 to infinity. Similarly, in a study addressing the risk of pancreatic cancer associated with cigarette smoking, a substantial modification of risk by diagnostic certainty was observed (Silverman et al., 1996). Improved general diagnostic accuracy and homogeneous histologic and molecular-level subgroups of pancreatic cancer are expected to allow for an improvement in the assessment of etiologic factors (Jones et al., 1991).

6.1.1 Case-control study

The cases were all deceased, implying a high rate of autopsy and histological verification, thereby an enhancing diagnostic quality over preoperative diagnosis only. All endocrine pancreatic cancers were excluded (N=8).

Using cancer controls was based on the requirement of non-differential misclassification of determinant information. The control sites were selected to represent cancers with minimal occupational etiology. The selection was considered to increase the validity of the control entity, namely, representativeness of the controls in the industrial and occupational distributions of the source population, that is, occupationally active population. Use of cancer controls may result in effect masking if the control cancer shares an etiologic agent with the type of cancer under study. The likelihood of at least some exposures falling into this category cannot thus be ruled out.

Homogeneity of exposures is a prerequisite for meaningful determinant categories but is subject to tradeoff with study size. It presumably varied between branch, job and agent entities. Detailed more homogeneous categories could not be used, as the numbers would have dwindled rapidly. Three levels (light/moderate/heavy) were therefore adopted. Number of exposed cases varied by agent.

Forcing a number of potential confounders into the models controlled confounding. The major known confounders present in these data are included in the models, with the exception of diet, which was considered too unreliable to be ascertained in retrospect from the next-of-kin in a mail questionnaire. The dichotomous (yes/no in the 1960s) smoking variable may have left some residual confounding from smoking in some of the comparisons. Overall, confounding and control of confounding in studies of pancreatic cancer may present uncertainties, since the causes of this cancer are to an overwhelming degree unknown.

Nonresponse would bias results if it associated with the determinants under study. Response rate presumably depends on age, gender, and relation to study subject of the responder. The distributions of the responders in their relation to the study subjects were very similar between the cases and controls. This fact, combined with highly comparable age and gender distributions between the cases and the controls, and with the restriction that both the cases and the controls were decedents and contemporaneously diagnosed for cancer, makes it unlikely that response induced any serious asymmetry in response; hence, the likelihood of a serious bias in the results is low, and the major effect of response is reduction of effective study size.

In case-control studies of pancreatic cancer, it is difficult to avoid the use of proxy responders (Gold et al., 1985; Mack et al., 1986; Farrow and Davis, 1990), except in hospital-based prospective case-control studies (Clavel et al., 1989). The information provided by the next-of-skin is deficient to an unknown degree. Precision and accuracy may vary by branch, job title, number of jobs held by the study subjects, and time elapsed from job assignment to questionnaire administration and, in addition, by age, gender, and relation to the subject of the responder. It has been reported (Lerchen and Samet, 1986) that wives may not completely report lifetime occupational histories provided by their husbands, but agreement improved substantially for reporting of the longest job held, which, in essence, was the one of interest in the present study. As all subjects for the present study were deceased cancer cases, we believe that the error distribution in the proxy information on job histories and confounders are similar between the cases and the controls. In both responses it may have an effect on the results and this is the weakness of this study. The implication is that any imperfections arising from a surrogate source of information would seem to add to overall imprecision of the occupational data, and some high excess risks may have been missed because of nondifferential errors. This may be compounded by the fact that we used a mail questionnaire, not a personal interview.

6.1.2 Meta-analysis

Meta-analysis of non-experimental studies is becoming as common as of clinical trials. Several articles have discussed problems in non-experimental data (Morris, 1994; Wong and Raabe, 1998; Egger et al., 1998; Myers and Thompson, 1998). Most of occupational meta-analyses are aggregated non-experimental studies, usually cohort and/or case-control studies (McElvenny et al., 2004). Aggregating non-experimental studies, the main problems are combinability and heterogeneity of studies, study selection bias, publication bias, ecological bias, and confounding. Some meta-analyses reported between-study heterogeneity and yet used fixed effects models only, instead of random effects models.

Combinability and heterogeneity

Epidemiologic meta-analyses have imperfect combinability of results associated with different study types, methods, populations, exposure parameters and circumstances, and diagnostic specificities. In the meta-analyses, MRRs were calculated excluding the poor quality studies which represented proportional studies in the study design. Separate MRRs for cohort studies using internal controls, case-control studies, and SMR/SIR studies were calculated. Differences in results from different study types were not consistent. We therefore combined all study types in the hierarchical Bayesian meta-analysis. In the hierarchical Bayesian models, one covariate was study type (case-control vs. cohort).

Several studies were poorly characterized. There were even studies that did not specify whether the cohort consisted of men, women, or both. In the agent specific meta-analysis, the data were analyzed for known male and female relative risk estimates separately. Women were associated with slightly higher MRRs than men for chlorinated hydrocarbon compounds. There were only few studies for women in the job specific meta-analysis.

There was in all likelihood substantial heterogeneity across observed relative risk estimates in the quality and intensity of exposure and job title categories, in the intake route (respiratory, dermal, digestive) of exposure, time aspects of exposure (period, latency, duration, and intensity), applied scales of exposure, as well as in the quality of histological diagnosis of pancreatic cancer. Qualitative and quantitative differences in exposures have already been exemplified in connection with chlorinated hydrocarbon compounds and insecticides. Random effects models were used avoiding between-study heterogeneity. Based on a rough statistical test, heterogeneity in the estimates of relative risks was found for studies addressing to asbestos, electromagnetic fields, chlorinated hydrocarbon compounds, and man-made vitreous fibers in the agent specific study, and asphalt workers, farmers, painters and sawyers in the job specific study. As exposure levels were unknown, the problem of combining for different exposure levels and time parameters of exposure remain. These may weaken the results.

Some studies did not document exposure aspects at all, and no study provided a comprehensive documentation. Expert assessment, which represents an acceptable method of exposure assessment, was used in 25 relative risk estimates. Industrial hygiene measurements that represent a certain degree of objectivity were used as the prime source of exposure data in only four relative risk estimates. Exposure assessment based on job titles (57 relative risk estimates) is of lower quality, unless exposures happen to be highly homogeneous within job titles. In fact, some of the relative risk estimates represented rather homogeneous single-title cohorts.

Job exposure matrices (JEM) assess exposures better if the matrix is specific for branch, job title and even for company and time period. JEMs of variable degree of specificity were applied in 15 observed relative risk estimates. Most were relatively unspecific and thereby induced exposure misclassification. Misclassification, however, was likely to be non-differential, resulting in a tendency toward underestimation of the excess MRRs. However, Björk and Strömberg (2002) have reported that misclassification bias can occur in either direction. Multiple sources of exposure data were applied in 37 relative risk estimates. Agent specific and job title specific data were longitudinal in 128 and 112 relative risk estimates and lifelong in 47 and 4 relative risk estimates, respectively. The longitudinality of agents and job titles was thus well covered.

Misclassification rates for pancreatic cancer are marked, as noted earlier. In the agent specific meta-analyses, MRRs were higher for nine but lower for 10 relative risk estimates in which histological verification was applied, compared with no histological verification. Few job title studies had histological verification. In the simple job title RE meta-analyses, job specific MRRs were higher in eight and lower in seven relative risk estimates in which histological was applied (unpublished results). The results of meta-analyses did not differ between histological and non-histological diagnoses of pancreatic cancer.

Publication bias

Nonpositive occupational findings from small studies were not likely to remain unpublished. Publication bias is not likely in this study, as very few small studies expressly considered the occupational determinants of pancreatic cancer. Publication bias was suspected only for the job title studies addressing metal plating workers and so that small high risk studies were unpublished. The agent studies did not show publication bias for any agent.

A counterargument may however be raised about cohort studies with multiple end-points. Some of these studies deleted results based on small numbers, occasionally for pancreatic cancer. This omission may have minor influence on the results of meta-analyses. Some case-control studies may have omitted results for rare exposures, with similar minor effect on the results of meta-analyses.

Selection of studies

Major databases and lists of references of the studies were used for identifying of studies in any language. Studies not found in major databases are probably of low quality. Unpublished studies were not attempted to identify. The selection of studies did not be comprehensive lacking unpublished studies but it was consistent.

Extraction

Extractor bias was minimized by the formal extraction procedure between the group of extractors and the central checking of the extraction. The procedure was also intended to guarantee the extraction of the relevant relative risk estimates in studies that offered several alternative relative risk estimates.

Reference populations

Not all observed relative risk estimates in the data were strictly independent because in some studies an internal unexposed industrial population was used as the common reference for more than one exposed population. This was rare, however, and we consider the ensuing bias in the precision of MRR minimal. Reference populations are a problem in proportional studies, where the population basis is unknown. For most analyses, we excluded proportional studies for this reason. Comparability of relative risk estimates may be a problem in SMR and SIR studies because of the healthy worker effect. It is unknown to what extent the healthy worker effect and its components might have biased the results of meta-analysis.

Confounding

Control of confounding is a problem in studies of pancreatic cancer, as tobacco smoking and diabetes are the only known common causes of this malignancy. Even a rough measurement of confounding bias is difficult. Case-control studies are in principle best equipped for adjustment for confounders. Several of these studies did adjust for various factors. In other study types, adjustment was rare. Attempts to aggregate results over studies that adjusted for smoking failed because of small number of such studies. The number of adjusted relative risk estimates ranged from zero to two across the occupational agents. In all hierarchical Bayesian models for meta-analysis, confounding was controlled by forcing five potential confounders into the models.

Ecological bias

Ecological or aggregated bias may emerge when using group level data for inferences on the individual level. Because, for instance whole group of exposed workers exposures as same proportion to occupational agents according JEM, it does not take account of the individual deviations. Ecological bias in average weakens relative risks (Gilks and Richardson, 1992).

In Study IV, the hierarchical Bayesian models operated on three levels: observed relative risk estimates from studies, group of job titles, and agents of exposure. An ecological bias may appear when proportions of agents from FINJEM observed at the job title level are applied to the relative risk estimates level. Two-level hierarchical Bayesian meta-analysis has been applied for clinical trials, but applications on non-experimental data are rare. Hierarchical Bayesian methods in ecological studies, including the ecological bias, have been discussed (Morgenstern, 1998; Greenland, 2001; Richardson and Best, 2003; Wakefield, 2004; Jackson et al., 2006). Even a simple meta-analysis involves an ecological bias, as outcomes are not available on the individual level (Greenland, 1998). The hierarchical Bayesian meta-analysis (Study IV) involved studies of job titles with external agent data (FINJEM) with unknown extrapolability and unknown exposure levels, hence liable to exposure misclassification. Inclusion of country as a covariate in the hierarchical Bayesian models presumably reduced the misclassification bias.

6.2 Substance considerations of the results

6.2.1 Chlorinated hydrocarbon solvents and related compounds

In Study II, the excess risk found for chlorinated hydrocarbon compounds was based on 20 observed relative risk estimates. Heterogeneity of RRs bordered significance ($p = 0.05$) and may be explained by differences in the chemical structure and exposure level of the agents. In the hierarchical Bayesian meta-analysis (Study IV), the excess risk for CHC was also found based on exposures of three job titles, laundry and dry cleaning workers, metal plating workers, and printers/pressmen/newspaper workers, using the FINJEM interface for exposures assessment.

Various compounds with variable carcinogenic potential were analyzed in the study reports as worker exposures: trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, methylene chloride, vinyl chloride, ethylene chlorohydrine, ethylene dichloride, bis(chloromethyl)ether, and polychlorinated biphenyls. Intensities and long term doses were characterized in most of the studies either poorly or not at all. For individual chlorinated hydrocarbon solvents, indications for weak excesses were found for trichloroethylene, tetrachloroethylene, methylene chloride, vinyl chloride, polychlorinated biphenyls (PCBs), and chlorohydrin manufacture, but not for carbon tetrachloride. The highest excesses were found also for workers in two job title categories, which were exposed mostly to chlorinated hydrocarbon solvents: metal degreasing and related jobs, and dry cleaning. Excesses were high for printers/pressmen/newspaper workers in the non-Bayesian random effects meta-analyses.

Experimental cancer studies and epidemiological studies suggest that environmental PCB mixtures are likely to pose a risk of cancer to humans (IARC, 1987). A case-control study of pancreatic cancer (Hoppin et al., 2000) found an OR 4.2 (95% CI 1.9-9.4) for >360 vs. <185 ng/g PCB in blood lipid.). After closing our meta-analysis, May 1998, Kernan et al. (1999) have found a high excess risk for white female workers exposed to methylene chloride in their case-control study (OR 1.3; 95% CI 1.1-1.6).

In the meta-analyses, exposure to chlorinated hydrocarbon solvents and related compounds increased the risk of pancreatic cancer.

6.2.2 Insecticides

In Study II, the aggregated MRR for insecticides was 1.5 (95% CI 0.6 -3.7); in case-control studies it was 3.7 (0.3 to 43), based on the random effects model. The highest RR was obtained for exposure to DDT family (DDT, ethylan, DDD; OR 21.0; 95% CI 2.6-966; five exposed cases) in a case-control study nested in a chemical manufacturing cohort (Garabrant et al., 1993). Potential confounders included nitrophenol derivatives, clays, *N,N*-Dimethylformamide, dispersing agents, octane, and carbon tetrachloride. The other case-control study (Fryzek et al., 1997) was population based (Michigan, US), with self-reported exposures. Based on 21 exposed cases, it yielded an OR 1.5 (0.8 to 2.9) for organochlorine insecticides. Assuming an effect, the difference between the two point estimates might be due to qualitative and quantitative differences in exposures between manufacturing and agricultural application.

In the Bayesian meta-analysis, an excess risk for insecticides was found based on exposure in plywood/fiberboard workers. An excess risk for plywood/fiberboard workers was also found in the RE meta-analysis and in the HB meta-analysis.

After closing our meta-analysis, Beard et al. (2003) reported a high excess risk (SMR 5.3, 95% CI 1.1-15.4) for outdoor workers exposed to DDT in their cohort study. In this study, exposure to insecticides may increase risk of pancreatic cancer.

6.2.3 Nickel and nickel compounds, and chromium and chromium compounds

In Study II, the risk for nickel and nickel compounds was most evident in population based case-control studies, including one high positive finding (OR 2.1; 95% CI 1.2-3.8) (Siemiatycki et al., 1991). In hierarchical Bayesian meta-analysis, the excess risk was not found (based on exposure of seven job titles; fitter/assemblers, foundry workers, machine/engine mechanics, metal plating, metal smelting furnacemen, sheet metal workers, and turners/toolmakers/machine tool setters, by the FINJEM data). In the non-Bayesian random effects meta-analysis, the MRRs for these job titles ranged from 0.7 to 2.04, the lowest MRRs were for job titles on which workers were only exposed to nickel. Workers on the other job titles were exposed also some other agent(s) than nickel.

Weiderpass et al. (2003) reported a strong positive association between pancreatic cancer and exposure to nickel and nickel compounds in their Finnish female cohort study (RR 1.7; 95% CI 1.2-2.4). This study was not included in meta-analyses.

In Study II, the MRR for chromium and chromium compounds (1.4) was increased in all studies, including one high positive SMR finding (Franchini et al., 1983), but was not in excess in population-based case-control studies. In HB meta-analysis, nickel and chromium were combined, because the proportions of exposed workers were almost equivalent and the results were the same for both metals. Subsequently, Weiderpass et al. (2003) found a high excess of pancreatic cancer for chromium (RR 1.8; 95% CI 1.0-3.1) in Finnish women workers.

In this study, the results for exposure to nickel and nickel compounds were inconsistent.

6.2.4 Other agents

In Study II a weak increase was present for PAHs in all studies, in population based case-control studies, and in the two SMR/SIR studies. In HB meta-analysis the MRR for PAHs was 1.1 and 95% CrI (0.9-1.5). High positive findings were found in three studies (Romundstad et al., 2000a; Romundstad et al., 2000b; Weiderpass et al., 2003) after closing our meta-analysis.

The excess of silica dust reached significance in one (Study II) of three studies. Study II found a high excess for aliphatic and alicyclic hydrocarbon solvents. This finding was aggregated with the finding of no excess for alikeness (C_5-C_{17}) in another population based study from Montreal (Siemiatycki et al., 1991) the result being MRR 1.3 (95% CI; 0.8-2.0) and in the HB meta-analysis was 1.1.

7. CONCLUSIONS

1. Results of the case-control study suggest that heavy occupational exposure to organic solvents, especially to aliphatic hydrocarbon solvents, aromatic hydrocarbon solvents, and other solvents, but not chlorinated hydrocarbon solvents, may increase the risk of pancreatic cancer. Additional excess was found for exposure to ionizing radiation.

2. Results of the non-Bayesian and the Bayesian meta-analyses suggest that occupational exposure to some chlorinated hydrocarbon solvents and related compounds may increase the risk of pancreatic cancer. The finding was supported by high excesses from studies addressing metal degreasing and related jobs and dry cleaning. Additionally consistent excess risk was found for insecticides. Excesses associated with occupational exposure to nickel and nickel compounds were suggested in the random effects meta-analyses but not in the hierarchical Bayesian meta-analysis.

3. Hierarchical models used in this study are applicable in meta-analyses when studies addressing the agent(s) under study are lacking or very few, but several studies address job titles with potential exposure to these agents, and when studies addressing workers exposed to several agents. A job-exposure matrix or a formal expert assessment system is necessary in these situations. Hierarchical models for meta-analysis involving durations and intensities of exposure to occupational agents from job-exposure matrix should be developed.

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APPENDICES

APPENDIX 1.

Study ID: _______
Abstractor: ___________________________

☐ checked, date __/__ 199_

☐ entered, date __/__ 199_

Pancreas cancer meta study
Extraction form

N. Jourenkova, A. Ojajärvi, T. Partanen

Contents:

Form 1: Study characterization

Form 2: Estimate extraction

Exposure-specific data

Job title data

Form 1
STUDY CHARACTERIZATION

Characterize studies sent to you. Answer questions by circling appropriate code numbers. If results are presented for more than one population (e.g., subgroups such as race), fill in one form for each population.1.

Name of first author

____

2. Year of publication 19______

3. Country/countries

____

4. Study type (circle)
1 Administrative (linkage of administrative records, or PMR/MOR study)
2 Industrial cohort
3 Industry based (nested) case-control
4 Population or hospital based case-control

5. Cases
1 Exocrinic pancreas only
2 All pancreas cancers
3 Other, ______________________
4 Unspecified

6. Diagnosis of pancreas cancer cases
1 Histological
2 Other (clinical: radiology, autopsy, etc.)
3 Mortality files
4 Mixed
5 Unknown

7. Ascertainment of pancreas cancer cases
1 Mortality files
2 Cancer registry files
3 Hospital records
4 Other ______________________
5 Mixed
6 Unspecified

8. Reference ("unexposed") population **in administrative and industrial cohort studies**
1 Country/other large population
2 Local population
3 Internal
4 Several reference populations
5 Death/case distribution (PMR)
6 Other

9. Control selection **in case-control studies**
1 Population
2 Other cancers in population
3 Hospital controls
4 Other ______________________
5 Mixed or multiple control series

10. Follow-up period for case ascertainment from 19___ to 19___

11. Cohort and administrative studies:
Lost to follow-up
1 _____ %
2 unspecified

12. Case-control studies:
Response rate
Cases ______ %
Controls ______ %

13. Source of **exposure** data (if chemical/ physical exposures have been specified)

	yes	no
Industrial exposure measurements	1	2
Job-exposure matrix	1	2
Expert assessment	1	2
Job titles	1	2
Colleagues	1	2
Next-of-kin	1	2
Other ________________	1	2
Mixed	1	2
Unspecified	1	2

14. Time reference for **exposure**
1 Last or around diagnosis
2 Earlier cross-section
3 Lifetime longitudinal
4 Less than lifetime longitudinal
5 Other ________________
6 Unclear

15. Relative risk measure
1 SMR
2 SIR
3 PMR
4 PCMR
5 MOR
6 CMOR (Cancer mortality odds ratio)
7 HR (Hazard ratio)
8 OR
9 RR (ratio of risks or cumulative incidences in exposed and unexposed industrial cohorts)
0 MR (ratio of mortalities in exposed and unexposed industrial cohorts)

16. Cohort admission
1 At entry to exposure / employment
2 At cross section(s) during exposure / employment
3 Mixed
4 Not applicable

17. Give lag period(s) in years _________

18. Exposure response or employment-response analysis?
1 no
2 yes
Describe.
____
____
____

19. Job title from
1 Industry files (employment files)
2 Mortality file
3 Self-reported or proxy reported, fully or mainly self
4 Self-reported or proxy reported, fully or mainly proxy
5 Union files
6 Several sources

20. Time reference for **job title**
1 Last or around diagnosis
2 Earlier cross-section
3 Lifetime longitudinal
4 Less than lifetime longitudinal
5 Other __________________
6 Unclear

21. Job title coding (classification)
1 Standard international
2 National modification
3 Special (e.g., for industry)
4 Mixed
5 Unspecified

22. For which **job titles** are there results?
1 All main groups, how many _______
2 Only jobs with elevated risks
3 High and low but not medium-risk jobs
4 Otherwise selected (eg, narrow industrial cohort) ________________

Comments:

<u>Form 2</u>
Estimate extraction

Extract relevant estimates of relative risk. There are two different sections for estimate extraction: one for selected **exposures** (in case risks have been estimated for exposures), and another for selected **job titles**.

Extract measures of relative risks associated with specific exposures or job titles. Extract **the most unbiased estimate** if there is a choice. After reading carefully the paper, fill the form. Choose estimates adjusted for at least known risk factors for PC (age, gender, tobacco smoking), if there is a choice. Prefer social class adjusted RRs over RRs unadjusted for social class. Choose risk estimate nearest to 20-y latency period, if there is a choice.

Note that there are synonyms and there are closely related job titles. The alphabetic list in **Annex 1** tells you where to find them in the Job Title Data Table.

EXPOSURE-SPECIFIC DATA

Risk estimates adjusted for ____
Latency period ___________ years
P-VALUE ONLY IF CI IS NOT AVAILABLE

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Exposure	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
1. Aliphatic (hydrocarbon) solvents															
2. Animal dust															
3. Aromatic (hydrocarbon) solvents, benzene, styrene (<u>exclude</u> aromatic amines)															
4. Arsenic															
5. Asbestos, crocidolite															
6. Bitumen fumes, asphalt fumes															
7. Cadmium															
8. Chlorinated (hydrocarbon) solvents (eg, trichloroethylene, tetrachloroethylene = perchloroethylene), halogenated hydrocarbons, methylene chloride, vinyl chloride monomer															
9. Chromium, chromate pigments, ferrochromium															
10. Diesel engine exhaust or unspecified engine exhaust															
11. Env. tob. smoke at work															
12. Flour dust															
13. Formaldehyde															
14. Fungicides, fungus control agents, chlorophenols															
15. Gasoline (Am), petrol (Br)															
16. Gasoline engine exhaust															
17. Herbicides (chlorophenoxy, phenoxy), weed killers, defoliants															
18. Insecticides, insect control agents, or unspecified (organo-chlorine) pesticides, DBCP, DDT															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Exposure	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
19. Ionizing radiation, radon															
20. Iron															
21. Lead / lead compouds															
22. Low freq. (electro)magnetic fields, EMF															
23. Man-made mineral (vitreous) fibres, incl. mineral wool, MMMF, MMVF, rock-wool															
24. Nickel															
25. Oil mist, machining fluid, cutting fluid															
26. PAH (polyaromatics)															
27. Quartz (silica) dust															
28. Ultraviolet radiation															
29. Wood dust															

Comments:

JOB TITLE DATA

Risk estimates adjusted for ____
Latency period ___________ years
P-VALUE ONLY IF CI IS NOT AVAILABLE

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page
1. Airline captain/pilot															
2. Artist/display decorator/layout/ designer															
3. Asphalt worker/highway worker															
4. Assembler (machine/metalware)/ aircraft manufacturing worker/ worker in automobile engine and part manufacturing complex/worker in construction equipment and diesel engine manufacturing plant/ aircraft factory/automobile industry/ automotive engine manufacturing plant/capacitor manufacturing/ motor vehicle manufacturing/ worker employed in cable manufacture plant/worker in bearing manufacture plant															
5. Baker															
6. Basket/brush maker															
7. Bath attendant															
8. Beautician/cosmetologist															
9. Bench carpenter															
10. Bookbinder															
11. Brewer/brewerage maker/brewery worker															
12. Bricklayer/plasterer/tile setter															
13. Butcher/sausage maker/ slaughterer/meat worker/worker in meat department of supermarket															
14. Cabinetmaker/joiner															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
15. Cannery (tinnery) worker															
16. Charworker/cleaner/sewage plant worker															
17. Chimney sweep															
18. Chocolate/confectionery manufacturer															
19. Cold and hot metal rolling worker															
20. Concrete mixer operator/ concrete product worker/cement worker															
21. Concrete shutterer/finisher															
22. Construction carpenter															
23. Construction machine operator/ heavy construction equipment operator															
24. Construction worker unspecified, construction laborer/ worker															
25. Cook, chef															
26. Cooker/furnaceman (chemical processing)															
27. Crane operator															
28. Crusher/grinder/calender operator (chem. processing)															
29. Customs officer/border guard															
30. Dairy worker/dairy cattle worker															
31. Distiller															
32. Electric machine operators															
33. Electric/electronic equipment assembler/transformer-assembly/ capacitor manufacturing worker/ carbon electrode manufacturing worker/ worker employed at transformer manufacturing plant/ battery manufacture/transformer manufacturing plant															
34. Electrician/electrical (utility) worker															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
35. Electronics/telecommunications workman/worker in tele-communication industry															
36. Farm/agricultural worker															
37. Farmer/dairy farmer/rice grower/ agriculture															
38. Fibre processor															
39. Fireman/fire fighter															
40. Fisher/fisherman															
41. Fitter/assembler															
42. Flight attendant/steward															
43. Forestry job															
44. Forklift operator															
45. Foundryman/primary aluminum foundry (worker)/ steel foundry worker															
46. Fur farmer															
47. Furrier/fur worker/fur industry															
48. Garden/park job/gardener/orchard worker															
49. Gasoline (service) station attendant/petrol pump attendant/ filling station attendant/person emloyed in fuel distribution/ petroleum marketing and distribution worker															
50. Glass moulder															
51. Glass/ceramics decorator/ dipper															
52. Glass/ceramics kilnman															
53. Glass/clay maker															
54. Glazier															
55. Goldsmith/silversmith															
56. Grain miller/corn wet-milling worker/ flour mill worker/worker in grain industry/flour industry															
57. Graphic occupation															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page
58. Hairdresser/barber															
59. Heat treater/hardener/temperer															
60. High voltage electric machine fitter															
61. Hotel/restaurant matron															
62. Housekeeper/home help/ caretaker/janitor															
63. Industrial sewer															
64. Insulation worker/insulator															
65. Jewellery job/ jewelry worker															
66. Kitchen assistant															
67. Knitting machine operator															
68. Laboratory/chemist															
69. Labourer															
70. Laundry/launderer/ dry cleaning job															
71. Leather sewer															
72. Lithographer															
73. Livestock breeder															
74. Lumberjack/logger															
75. Machine setter/rigger (not in textile)															
76. Machine (automobile) /engine mechanic/bus garage worker/ worker at aircraft maintenance facility															
77. Mailman/newspaper delivery															
78. Mail/tele work, other or unspecified															
79. Maintenance personal															
80. Metal plating/coating, chrome/ chromium plating worker/ metal components manufacturing worker/ nickel plater/ worker in die-casting and electroplating plant															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page
81. Metal smelting furnaceman/ aluminium (reduction plant)/coke plant/coke oven worker/worker producing ferroalloys and stainless steel/coke oven plant of Carrara/ Copper smelter/ferroalloy industry															
82. Milliner/hatmaker															
83. Miner (coal/gold/uranium)/shot firer/ quarry/rock salt worker/rubber worker/worker mining and milling attapulgite clay															
84. Mineral processing															
85. Motor vehicle driver (taxi, truck, tractor, lorry, van, bus, coach)/ teamster/professional driver															
86. Moulder															
87. Nurse/nursing assist/attendant															
88. Office receptionist/messenger															
89. Optician															
90. Packer/labeller															
91. Painter (art)															
92. Painter/lacquered/floor layer															
93. Paper product worker															
94. Paper/cardboard mill worker/ cellulose fiber production worker/ cellulose triacetate-fiber worker/ pulp and paper mill worker															
95. Pharmacy job/pharmaceutical worker/pharmacy technician/ pharmaceutical plant															
96. Photographer/cameraman															
97. Photographic laboratory assistant															
98. Physician/dentist															
99. Plastic product worker/plastic manufacturing industry															
100. Plumber/pipefitter															
101. Plywood/fibreboard worker															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page	RR	__ % CI	p (tail)	N obs. cases	from page
102. Policeman															
103. Potter															
104. Precision instrument maker															
105. Printer/pressman/newspaper worker/newspaper web pressman/ printing industry															
106. Processed food maker															
107. Pulp mill worker															
108. Radio/TV transmitter															
109. Railway engine															
110. Railway personal, other, unspecified															
111. Refinery worker/oil (refinery) worker/ petrochemical worker/ petroleum refinery and chemical plant worker/producing and pipeline worker/worker from petroleum refineries/worker in petroleum manufacturing and distribution industry/Mobil Corporation/oil distribution centre (UK) /oil industry/oil refinery/ petroleum industry															
112. Reinforced concrete layer/ stone-mason/construction ironworker															
113. Rod layer															
114. Rubber production worker/curing worker (rubber)/ reclaim worker (rubber)/rubber (tyre) industry															
115. Salesman; sales worker, commercial traveler															
116. Sawyer															
117. Seafarer, sailor, seaman, deckhand															
118. Sheet metal worker															
119. Shoe sewer															
120. Shoemaker/worker/ repairer															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
121. Shop job															
122. Smith															
123. Sole fitter															
124. Spinning operator															
125. Stationary engine/machinery operator															
126. Stevedore															
127. Stone/granite cutter															
128. Sugar processing worker															
129. Tanner/fellmonger/dresser/ tannery worker/leather tanner/ leather worker/ leather tanning industry/ tanning industry															
130. Taylor/seamstress/garment industry															
131. Telephone installer/lineman/ cable jointer/repairman															
132. Textile finisher/dyer/dyestuffs worker															
133. Textile inspector															
134. Textile machine setter operator															
135. Textile/leather patternmaker/ cutter															
136. Timberman/lumberman															
137. Tobacco industry worker															
138. Turner/toolmaker/machine tool setter															
139. Typist/data clerk/computing															
140. Typographer															
141. Upholster															
142. Waiter/waitress/bartender															
143. Warehouseman															
144. Watchmaker															
145. Weaving machine operator, carpet worker															
146. Welder (arc)/steel welder/ flame cutter/															

	MEN					WOMEN					MEN + WOMEN OR UNSPECIFIED				
Job title	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page	RR	___ % CI	p (tail)	N obs. cases	from page
147. Wire/pipe drawer															
148. Wood grinder															
149. Wooden surface finisher															
150. Woodworking machine operator/ wood worker/furniture maker															

Comments:

APPENDIX 2.

Job title	Proportion exposed to chemical agent							
	ALHC	CHC	FUNG	INSC	NI/CR	PAH	SIL	WOOD
Asphalt workers	-	-	-	-	-	0.72	-	-
Bench carpenters	-	-	-	-	-	-	-	1
Bricklayers	-	-	-	-	-	-	1	-
Cabinet makers	-	-	-	-	-	-	-	1
Cement workers	-	-	-	-	-	-	1	-
Concrete shutters	-	-	-	-	-	-	0.90	-
Construction carpenters	-	-	-	-	-	-	0.76	1
Construction workers	-	-	-	-	-	-	0.22	-
Electric machine operators	-	-	-	-	-	-	0.29	-
Farmers	-	-	0.25	-	-	-	-	-
Fitters/assemblers	-	-	-	-	0.42	-	-	-
Foundry workers	-	-	-	-	0.25	-	0.44	-
Laundry and dry cleaning workers	-	0.39	-	-	-	-	-	-
Machine/engine mechanics	-	-	-	-	0.33	1	-	-
Metal plating workers	-	0.92	-	-	0.46	-	-	-
Metal smelting furnacemen	-	-	-	-	0.41	1	1	-
Miners	-	-	-	-	-	1	1	-
Painters	0.98	-	-	-	-	-	-	-
Plywood/fiberboard workers	-	-	0.33	0.33	-	-	-	0.66
Printers/pressmen/newspaper workers	0.33	0.20	-	-	-	-	-	-
Saywers	-	-	0.45	-	-	-	-	1
Sheet metal workers	-	-	-	-	0.38	-	-	-
Smiths	-	-	-	-	-	1	-	-
Stone cutters	-	-	-	-	-	-	0.87	-
Timbermen/lumbermen	-	-	-	-	-	-	-	0.56
Turners/toolmakers/ machine-tool setters	-	-	-	-	0.50	1	-	-
Wood working machine operators	-	-	-	-	-	-	-	1

ALHC = aliphatic and alicyclic hydrocarbon solvents, CHC = chlorinated hydrocarbon compounds, FUNG = fungicides, INSC = insecticides, NI/CR = nickel/chromium, PAH = polycyclic aromatic hydrocarbons, SIL = silica dust, WOOD = wood dust, - = proportion exopesed is zero

APPENDIX 3.

AGENT
STUDY TYPE
Study RR 95 % CI Weight
Results of meta-analysis: ***MRR*** ***95% CI***
Heterogeneity

ALIPHATIC AND ALICYCLIC HYDROCARBON SOLVENTS:

OR:

Study	RR	95 % CI	Weight
Study I (1995)	1.6	1.0 - 2.6	19.1
Siemiatycki (1991)	1.0	0.7 - 1.4	32.0

Aggregate (OR studies): 1.3 0.8 – 2.0
χ_1^2 = 2.9 p =0.09

ANIMAL DUST:

[PMR:

Magnani et al. (1987) 1.0 0.6 - 1.6]

AROMATIC HYDROCARBON SOLVENTS:

OR:

Study	RR	95 % CI	Weight
Greenland et al. (1994)	0.6	0.2 - 1.9	2.7
Study I (1995)	1.8	1.1 - 2.8	18.1
Mack et al. (1985)	0.6	0.3 - 1.2	8.0
Siemiatycki (1991)	0.8	0.5 - 1.4	14.5

Aggregate (OR studies): 0.9 0.5 - 1.6
χ_3^2 = 9.7 p < 0.05

SIR / SMR:

Study	RR	95 % CI	Weight
Acquavella et al. (1993)	2.9	0.1 - 16	0.6
Anttila et al. (1998)	1.3	0.4 - 2.9	4.0
Bond et al (1992)	0.5	0.2 - 1.1	4.0
Decoufle et al. (1983)	1.6	0.0 - 5.6	0.6
Frentzel-Beyme (1978)	2.8	0.3 - 10.2	1.3
Kogevinas et al. (1994)	1.1	0.8 - 1.5	30.8
Sathiakumar et al (1998)	0.7	0.4 - 1.2	12.2
Wong (1987)	0.9	0.4 - 1.8	6.7
Wong et al. (1994)	1.3	0.5 - 2.5	6.7

Aggregate (SIR / SMR studies): 1.0 0.8 - 1.3
χ_8^2 = 6. 6 p = 0.6

Aggregate (all studies): 1.0 0.8 - 1.3
χ_{12}^2 = 16.6 p = 0.2

[PMR:

Magnani et al. (1987) 1.2 0.9 - 1.7]

ARSENIC:

HR:

Tollestrup et al. (1995) 1.4 0.2 - 11.6 0.9

OR:

Study	RR	95 % CI	Weight
Mack et al. (1985)	1.0	0.3 - 5.5	3.6
Siemiatycki (1991)	1.2	0.4 - 3.8	3.0

Aggregate (OR studies): 1.1 0.5-2.7
χ_1^2 = 0.1 p = 0.8

Aggregate (OR and HR studies): 1.2 0.5 - 2.6
χ_2^2 = 0.1 p = 0.96

SMR:

Enterline (1995) 0.9 0.4 - 1.5 10.3

Aggregate (all studies): 1.0 0.6 - 1.6
χ_3^2 = 0.4 p = 0.9

ASBESTOS:

OR:

Study	RR	95 % CI	Weight
Greenland et al. (1994)	0.8	0.4 - 1.8	6.4
Study I (1995)	0.6	0.5 - 1.0	29.3
Mack et al. (1985)	0.5	0.2 - 1.2	4.8
Siemiatycki (1991)	1.3	0.6 - 2.7	6.8

Aggregate (OR studies) 0.7 0.5 - 1.0
χ_3^2 =4.4 p=0.2

SIR / SMR:

Study	RR	95 % CI	Weight
Acheson et al. (1984)	1.0	0.8 - 1.2	115
Armstrong et al. (1979)	1.2	0.6 - 2.6	7.0
Brown et al. (1994)			
White: Men	1.5	0.6 - 3.0	5.8
Women	0.7	0.2 - 1.8	3.0
Black: Men	1.3	0.3 - 3.3	3.0
Cammarano et al. (1986)	3.6	0.1 - 19.9	0.4
Dement et al. (1994)			
Men	1.5	0.7 - 2.7	9.4
Women	1.0	0.3 - 2.5	3.0
Enterline et al. (1987)	1.1	0.5 - 2.1	6.5
Gustavsson and Reuterwall (1990)	0.6	0.1 - 2.1	1.2
Magnani et al. (1996)			
Men	1.1	0.5 - 2.1	7.5
Women	0.5	0.0 - 2.9	0.5
McDonald et al. (1993)	1.1	0.8 - 1.4	36.9
Ohlson et al. (1984)	1.1	0.6 - 1.9	11.3
Seidman et al. (1986)	2.3	1.1 - 4.5	7.3
Selikoff and Seidman (1981)	2.8	1.8 - 4.2	20.7
Sun et al. (1997)	1.4	0.6 - 2.9	5.7
Tsai et al. (1996)	0.7	0.3 - 1.4	6.6
Wilczynska et al. (1996)	1.1	0.4 - 2.3	4.9
Woitowitz et al. (1986)	1.6	0.4 - 4.1	3.0

Aggregate (SIR / SMR studies): 1.2 1.0 - 1.5
χ_{19}^2 = 28.9 p = 0.1

Aggregate (all studies): 1.1 0.9 - 1.4
χ_{23}^2 = 44.8 p< 0.01

[PMR:

Magnani et al. (1987) 0.9 0.7 - 1.2]

CADMIUM:

OR:
Study I (1995) 0.8 0.2 - 2.9 2.2
SMR:
Elinder et al. (1985) 0.7 0.3 - 1.4 5.8
Aggregate (all studies): 0.7 0.4 - 1.4
$\chi_1^2 = 0.03$ $p = 0.9$
[PMR:
Magnani et al. (1987) 1.3 0.9 - 1.8]

CHLORINATED HYDROCARBON SOLVENTS AND RELATED COMPOUNDS:

OR:
Greenland et al. (1995) 1.6 0.8 - 3.3 8.0
Siemiatycki (1991)
Chlorinated alkanes 0.8 0.4 - 1.5 5.5
Chlorinated alkenes 0.9 0.3 - 2.6 2.3
Aggregate (OR studies): 1.2 0.7 - 1.9
$\chi_2^2 = 1.9$ $p = 0.4$
IRR:
Hearne et al. (1990) 2.6 1.0 - 5.3 5.7
Aggregate (OR and IRR studies): 1.4 0.8 - 2.4
$\chi_3^2 = 4.4$ $p = 0.2$
SIR/ SMR:
Anttila et al. (1995) 2.0 1.0 - 3.7 9.5
Axelson et al. (1994) 0.3 0.0 - 1.4 0.6
Benson and Teta (1993) 4.9 1.6 - 11.4 3.9
Brown (1987)
Men 0.6 0.0 - 3.5 0.5
Women 0.5 0.0 - 2.7 0.5
Gibbs et al. (1996)
Men 0.6 0.1 - 1.7 2.2
Women 0.5 0.0 - 2.9 0.5
Lanes et al. (1993) 0.8 0.1 - 3.0 1.3
Nakamura (1983) 2.9 0.6 - 8.4 2.1
Sinks et al. (1992) 0.7 0.1 - 2.5 1.5
Simonato et al. (1991) 0.7 0.1 - 2.0 2.1
Smulevich et al. (1988) 1.7 0.4 - 5.0 2.2
Spirtas et al. (1991) 0.8 0.5 - 1.4 12.1
Tomenson et al. (1997) 1.0 0.2 - 2.1 2.2
Wong et al. (1991) 1.0 0.5 - 1.8 9.4
Yassi et al. (1994) 4.4 1.5 - 10.9 3.9
Aggregate
(SIR/SMR studies): 1.3 0.9 - 2.0
$\chi_{15}^2 = 25.3$ $p < 0.05$
Aggregate (all studies): 1.4 1.0 - 1.8
$\chi_{19}^2 = 29.9$ $p = 0.05$
[PMR:
Chiazzi and Ferenze (1981)
Men 1.1 0.8 - 1.6
Women 1.2 0.5 – 2.4
Magnani et al. (1987)
Carbon tetrachloride 1.1 0.8 - 1.5
Polychlorinated biphenyls 0.9 0.6 – 1.4]

CHROMIUM AND CHROMIUM COMPOUNDS:

OR
Study I (1995) 0.9 0.4 -2.0 5.7
Mack et al. (1985) 1.1 0.4 - 3.5 3.3
Siemiatycki (1991) 1.1 0.6 - 2.0 10.6
Aggregate (OR studies): 1.0 0.7 - 1.6
$\chi_2^2 = 0.3$ $p = 0.9$
SIR / SMR:
Axelsson et al. (1980) 0.6 0.0 - 3.5 0.5
Cammarano et al. (1986) 3.6 0.1 - 19.90.4
Franchini et al. (1983) 20.0 2.3 - 72.21.2
Kano et al. (1993) 1.0 0.0 - 5.6 0.6
Langård et al. (1990) 1.6 0.3 - 4.6 2.2
Sheffet et al. (1982) 1.5 0.6 - 3.1 5.8
Aggregate (SIR / SMR studies): 2.3 0.9 - 5.8
$\chi_5^2 = 8.4$ $p = 0.1$
Aggregate (all studies): 1.4 0.9 - 2.3
$\chi_8^2 = 11.8$ $p = 0.2$
[PMR:
Magnani et al. (1987) 1.3 1.0 - 1.7]

DIESEL ENGINE EXHAUST:

OR:
Study I (1995) 0.9 0.5 - 1.5 12.7
Mack et al. (1985) 0.5 0.2 - 1.2 4.8
Siemiatycki (1991) 1.1 0.9 - 1.3 115
Aggregate (OR studies): 1.0 0.7 - 1.3
$\chi_2^2 = 3.2$ $p = 0.2$
RR:
Boffetta et al. (1988) 1.4 0.9 - 2.0 24.5
HR:
Van Den Eeden
and Friedman (1993) 1.4 0.9 - 2.3 15.3
Aggregate (RR and HR studies):1.4 1.3 - 1.9
$\chi_1^2 = 0.0$ $p = 0.9$
Aggregate
(RR, HR and OR studies): 1.1 0.9 - 1.4
$\chi_4^2 = 5.8$ $p = 0.2$
SIR / SMR:
Gustavsson and
Reuterwall (1990) 0.6 0.1 - 2.1 1.2
Howe et al. (1983) 0.9 0.8 - 1.1 198
Aggregate (SIR / SMR studies): 0.9 0.8 - 1.1
$\chi_1^2 = 0.3$ $p = 0.6$
Aggregate (all studies): 1.0 0.9 - 1.2
$\chi_6^2 = 9.4$ $p = 0.2$

ELECTROMAGNETIC FIELDS:

SIR / SMR :

Baris et al. (1996)	2.4	0.8 - 6.9	3.3
Milham (1988)	0.6	0.4 - 0.9	23.7
Milham (1985)	1.1	0.8 - 1.5	38.9
Tynes et al. (1992)	1.2	1.0 - 1.4	158
Tynes et al (1994)	1.2	0.7 - 1.8	16.0

Aggregate (all studies:) 1.1 0.8 - 1.4

χ_4^2 = 9.8 $p < 0.05$

[PMR:

Magnani et al. (1987) 1.0 0.6 - 1.5]

FLOUR DUST:

OR:

Siemiatycki /1991 1.1 0.3 – 3.2

[PMR:

Magnani et al. (1987) 0.9 0.4 - 1.9]

FORMALDEHYDE:

OR:

Study I (1995)	0.6	0.3 -1.4	6.0
Siemiatycki (1991)	0.5	0.3 - 1.0	10.6

Aggregate (OR studies): 0.5 0.3 - 1.6

χ_2^2 = 4.7 $p = 0.1$

SMR:

Gardner et al. (1993)	1.0	0.7 - 1.4	32.0
Levine et al. (1984)	1.0	0.3 - 2.6	3.1
Stayner et al. (1988)	0.5	0.2 - 1.2	3.9

Aggregate (SMR studies): 0.9 0.7 - 1.3

χ_2^2 = 1.4 $p = 0.5$

Aggregate (all studies): 0.8 0.5 - 1.0

χ_4^2 = 6.5 $p = 0.3$

[PMR:

Hansen and Olsen (1996) 1.1 0.3 –3.2

Magnani et al. (1987) 0.9 0.4 - 1.9]

FUNGICIDES:

OR:

Study I (1995) 1.4 0.3 - 7.2 1.4

RR:

Ramlow et al. (1996) 1.3 0.3 - 5.0 2.0

Aggregate (all studies): 1.3 0.4 - 3.8

χ_1^2 = 0.0 $p = 0.9$

GASOLINE:

OR:

Study I (1995)	0.7	0.3 - 1.6	6.7
Siemiatycki (1991)	1.1	0.8 - 1.5	38.9

Aggregate (OR studies): 1.0 0.8 - 1.4

χ_1^2 = 1.0 $p = 0.3$

SMR:

Lynge et al. (1997)

Men	0.9	0.6 - 1.2	32.0
Women	0.2	0.0 - 1.3	1.6

Aggregate (SMR studies): 0.9 0.6 - 1.3

χ_1^2 = 0.9 $p = 0.5$

Aggregate (all studies): 1.0 0.8 - 1.2

χ_3^2 = 2.4 $p = 0.5$

HERBICIDES:

OR:

Fryzek et al. (1997) 0.9 0.7 - 1.8 17.2

SIR / SMR:

Asp et al. (1994)	1.1	0.3 - 2.8	3.1
Coggon et al. (1986)	0.7	0.3 - 1.4	7.6
Hooiveld et al. (1998)	2.5	0.7 - 6.3	3.2
Kogevinas et al. (1997)	0.9	0.7 - 1.3	43.5
Leet et al. (1996)	5.9	0.1 - 32.7	0.4
Lynge (1985)	0.6	0.1 - 1.7	2.2
Ott et al. (1987)	0.7	0.1 - 2.0	2.1
Sathiakumar et al. (1996)	1.8	0.4 - 5.3	2.1
Swaen et al (1992)	3.5	0.7 - 10.1	2.2

Aggregate (SIR / SMR studies): 1.1 0.8 - 1.5

χ_8^2 = 9.9 $p = 0.3$

Aggregate (all studies): 1.0 0.8 - 1.3

χ_9^2 = 10.1 $p = 0.3$

[PMR:

Magnani et al. (1987) 0.7 0.3 - 1.5]

INSECTICIDES:

OR:

Fryzek et al. (1997)	1.5	0.8 - 2.9	9.3
Garabrant et al. (1993)	21.0	2.6 - 966	0.4

Aggregate (OR studies): 3.7 0.3 - 43.3

χ_1^2 = 2.9 $p = 0.1$

SIR / SMR :

Brown (1992) 0.8 0.3 - 1.7 5.8

Aggregate (all studies:) 1.5 0.6 - 3.7

χ_2^2 = 4.3 $p = 0.1$

[PMR:

Cocco et al. (1997a) 0.6 0.1 - 1.6]

IRON AND IRON COMPOUNDS:

OR:

Siemiatycki (1991) 1.3 0.7 – 2.5

LEAD AND LEAD COMPOUNDS:

HR:

Tollestrup et al. (1995) 1.4 0.1 - 11.6 0.9

OR:

Study I (1995)	1.2	0.7 - 1.9	17.3
Siemiatycki (1991)	1.1	0.7 - 1.7	19.5

Aggregate (OR studies): ***1.1 0.8 - 1.6***
χ_1^2 = 0.1 p = 0.80

Aggregate (HR and OR studies): 1.1 0.8 - 1.6
χ_2^2 = 0.1 p=1.0

SMR:

Cocco et al. (1997b) 1.0 0.4 - 2.1 5.8

Aggregate (all studies): ***1.1 0.8 - 1.5***
χ_3^2 = 0.2 p=1.0

[PMR:

Magnani et al. (1987) 1.7 1.0 – 2.9]

MAN-MADE VITREOUS FIBERS:

OR:

Study I (1995)	0.8	0.5 - 1.3	16.8
Mack et al. (1985)	0.3	0.1 - 0.8	3.55
Siemiatycki (1991)	1.4	0.6 - 3.1	5.70

Aggregate (OR studies): ***0.8 0.4 - 1.5***
χ_2^2 = 5.2 p = 0 1

RR:

Claude and Frentzel-Beyme (1986) 6.8 1.0 - 45.2 1.1

Aggregate (OR and RR studies): 0.9 0.4 - 2.2
χ_3^2 = 9.9 p < 0.05

SMR:

Boffetta et al. (1997) 1.1 0.8 - 1.5 37.5

Aggregate (all studies): ***1.0 0.6 - 1.6***
χ42 = 10.7 p < 0.05

NICKEL:

OR:

Mack et al. (1985)	1.5	0.4 - 5.7	2.2
Siemiatycki (1991)	2.1	1.2 - 3.8	11.6

Aggregate (OR studies): ***2.0 1.2 - 3.2***
χ_1^2 = 0.2 p = 0.6

SMR:

Andersson et al. (1985)	1.2	0.01 - 6.2	0.4
Cammarano et al. (1986)	3.6	0 . 1 - 19.9	0.4
Shannon et al. (1991)	1.3	0.7 - 2.3	10.5

Aggregate (SMR studies): 1.3 0.8 - 2.4
χ_2 = 0.4 p = 0.8

Aggregate (all studies): ***1.7 1.1 - 2.5***
χ_4^2 = 1.6 p = 0.8

OIL MIST:

OR:

Bardin et al. (1997)	1.0	0.8 - 1.3	61.3
Greenland et al. (1994)	0.8	0.4 - 1.5	7.9
Mack et al. (1985)	0.5	0.2 - 1.0	5.9

Aggregate (OR studies): ***0.8 0.6 - 1.3***
χ_2^2 = 3.3 p = 0.2

SMR:

Acquavella et al. (1993)	0.7	0.1 - 2.6	1.5
Decoufle (1978)	0.3	0.0 - 1.5	0.4
Tolbert et al. (1992)	0.9	0.7 - 1.0	134

Aggregate (SMR studies): 0.9 0.7 - 1.0
χ_2^2 = 0.6 p = 0.8

Aggregate (all studies): ***0.9 0.8 - 1.0***
χ_5^2 = 4.4 p = 0.5

[PMR:

Park and Mirer (1996) 3.6 1.0 – 12.6]

POLYAROMATIC HYDROCARBONS:

OR:

Study I (1995)	1.3	0.7 - 2.6	8.9
Siemiatycki (1991)	1.4	0.6 - 3.1	5.7

Aggregate (OR studies): ***1.4 0.8 - 2.3***
χ_1^2 = 0.01 p = 0.9

SIR / SMR:

Cammarano et al. (1986)	3.6	0.1 - 19.9	0.4
Moulin et al. (1989)	2.8	0.3 - 10.2	1.3

Aggregate (SIR / SMR studies): 3.0 0.7 - 13.2
χ_1^2 = 0.0 p = 0.9

Aggregate(all studies): ***1.5 0.9 - 2.4***
χ_3^2 = 1.0 p = 0.8

SILICA DUST:

OR:

Study I (1995)	2.0	1.2 - 3.5	12.9
Siemiatycki (1991)	1.1	0.7 - 1.8	17.2

Aggregate (OR studies): ***1.5 0.8 - 2.7***
χ_1^2 = 2.7 p = 0.1

SMR:

Checkoway et al. (1997) 1.2 0.6 - 2.1 8.4

Aggregate (all studies): ***1.4 0.9 - 2.0***
χ_2^2 = 3.0 p = 0.2

[PMR:

Magnani et al. (1987) 1.0 0.7 - 1.4]

WOOD DUST:

OR

Study I (1995)	1.3	0.8 - 2.1	15.5
Mack et al. (1985)	0.7	0.3 - 1.6	5.5
Mikoczy et al. (1996)	1.73	0.1 - 30.8	0.5
Siemiatycki (1991)	1.2	0.8 - 1.8	23.4

Aggregate (all studies): ***1.2 0.9 - 1.6***
χ_3^2 = 1.7 p = 0.6

[PMR:

Magnani et al. (1987) 1.4 0.7 – 2.7]

APPENDIX 4.

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